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Understanding clinically significant portal hypertension: An in-depth look at pathogenesis, diagnosis and treatment

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Abstract

The development of clinically significant portal hypertension (CSPH) represents one of the strongest predictive biomarkers for disease progression in patients with compensated advanced chronic liver disease (cACLD). Chronic liver injury triggers both intra- and extrahepatic mechanisms, giving rise to an increasing portal pressure and a self-perpetuating cycle with worsening risks of liver-related complications and mortality. Diagnosing CSPH becomes challenging in patients with advanced but compensated chronic liver disease where CSPH is not apparent clinically. Approximately 60% of patients with cACLD will have CSPH, representing a critical window for intervention to reduce portal pressure and prevent complications. The current gold standard for portal pressure measurement, the hepatic venous pressure gradient, is impractical for widespread use. Emerging diagnostic tools aim to address this limitation. Techniques such as endoscopic ultrasound-guided portal pressure gradient measurement, and noninvasive approaches using imaging methods, elastography (targeting liver and/or spleen) and serum markers, offer alternatives for CSPH detection, and moreover, can guide treatment decisions. Non-selective beta-blockers are known to reduce morbidity and mortality in patients with CSPH. Unfortunately, they remain the only approved therapy for CSPH and they are not effective in reducing portal pressure in all patients, highlighting the urgent need for additional therapeutic options as well as practical methods to evaluate treatment response. Recent innovations and ongoing research are steering the field toward a more personalized approach, where diagnosis, treatment and follow up are tailored to individual patient risk profiles. This evolution holds the potential to improve outcomes in patients with CSPH.

Keywords Portal hypertension, elastography, noninvasive test, beta-blockers

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Introduction

When chronic causes of liver disease, such as alcohol, viral hepatitis or metabolic syndrome, persist, liver injury may develop slowly and progress to fibrosis, and eventually to cirrhosis. This process is paralleled with the development of portal hypertension (PHT), i.e., increasing pressure in the portal vein that takes blood from the gastrointestinal system and spleen to the liver. PHT usually progresses without symptoms until it reaches a critical threshold, known as clinically significant portal hypertension (CSPH), when symptoms like ascites, variceal bleeding and encephalopathy can become apparent. These 3 manifestations define decompensated liver cirrhosis, and are accompanied by a dramatic reduction in median survival, from more than 12 years in compensated cirrhosis to less than 2 years in decompensated cirrhosis [1,2]. Cirrhosis currently accounts for 2 million deaths worldwide each year [3]. Therefore, it is imperative to identify patients

at risk for decompensation and mortality so that targeted (secondary) preventive measures can be implemented. Historically, the role of PHT in disease progression was largely overlooked; it was not until 1990, during the first international Baveno consensus meeting, that consensus definitions for PHT were established [4]. More than 30 years have passed since Baveno I, and 6 other Baveno meetings have followed, leading to an exponential increase in research regarding PHT. This research has refined the concept of CSPH, which now serves as one of the most robust predictive biomarkers for liver disease progression. Although a great deal of knowledge has been gained about PHT, much remains to be discovered. This review provides an overview of what is currently known and which areas still need exploration.

First things first: how does it develop?

Depending on the underlying level of impediment of flow in the portal system, PHT can be classified into 3 groups: pre-hepatic, intrahepatic and post-hepatic PHT. Intrahepatic PHT can be further divided into sinusoidal and presinusoidal PHT [5,6]. In western countries, the most common cause of PHT is cirrhosis, which causes sinusoidal PHT [5]. In this review, we focus mainly on sinusoidal PHT, but understanding other mechanisms leading to portal hypertension is vital in recognizing the pitfalls in diagnosing CSPH.

The development of PHT in cirrhosis is driven by both increased intrahepatic vascular resistance and enhanced splanchnic blood flow. Approximately 70% of this resistance is due to structural change, such as the formation of fibrous septa and regenerative nodules during tissue remodeling. The remaining 30% is attributed to functional factors, including intrahepatic vasoconstriction mediated by activated hepatic stellate cells transforming into contractile myofibroblasts, along with an imbalance between vasodilatory agents (e.g., nitric oxide, carbon monoxide) and vasoconstrictive agents (e.g., prostaglandins, endothelins, norepinephrine, angiotensin) [6-10]. The resulting increase in portal pressure drives the formation of collaterals or spontaneous portosystemic shunts (SPSS) in an effort to divert the blood flow from the portal vein. Additionally, PHT drives extrahepatic NO overproduction, and consequently splanchnic vasodilation, resulting in a decrease in effective circulating volume that triggers reflex activation of the renin–angiotensin system and the sympathetic nervous system. This gives rise to a compensatory hyperdynamic circulation, increasing splanchnic blood flow and worsening PHT, thus resulting in a vicious circle [7-9].

These drivers of PHT, both directly and indirectly, contribute to the development of various complications in cirrhosis. These include varices, variceal bleeding, ascites, hyponatremia, hepatorenal syndrome (HRS), portopulmonary hypertension, hepatopulmonary syndrome, and cirrhotic cardiomyopathy. Moreover, SPSS may exacerbate hepatic encephalopathy, elevated pressure in the splenic vein can lead to splenomegaly and thrombocytopenia, while increased pressure in the splanchnic system may promote bacterial translocation, potentially resulting in spontaneous bacterial peritonitis (SBP), or triggering acute-on-chronic liver failure [9,11,12]. It is therefore unsurprising that a higher portal pressure is associated with a worse prognosis [13,14].

To measure is to know: how do we diagnose CSPH?

PHT thus plays a crucial role in the development of complications and mortality in chronic liver disease. By definition, decompensated cirrhosis involves the presence of CSPH. Diagnosing CSPH in patients with advanced but compensated chronic liver disease—where CSPH is not apparent clinically—is challenging yet crucial, as this stage represents a critical window for intervention, given its significant impact on prognosis. Approximately 60% of patients with compensated advanced chronic liver disease (cACLD) will exhibit CSPH [15,16]. Various invasive and noninvasive diagnostic tools are available to identify CSPH, each with its strengths and limitations. This section compares these methods, while the key features are summarized in Tables 1 and 2.

Invasive portal pressure measurement

The most accurate method for measuring portal pressure is direct cannulation of the portal vein. Percutaneous puncture of the portal vein is technically challenging, especially in the context of cirrhosis and coagulation abnormalities, making this method impracticable and potentially hazardous for clinical use [17]. The portal vein can also be reached via the transvenous route by puncture of the femoral or jugular vein, after which a catheter is advanced through the inferior *vena cava* into the hepatic vein. The portal vein can be punctured from within the hepatic vein under radiologic guidance, but—except for patients receiving a transjugular intrahepatic portosystemic shunt (TIPS), where direct cannulation of the portal vein is necessary for therapeutic reasons—this method is again too invasive for use as a purely diagnostic tool. Therefore, an indirect approach to the portal vein was developed, called the *hepatic-venous portal gradient (HVPG) measurement*.

The HVPG is typically measured by an experienced interventional radiologist or hepatologist. A balloon-tipped catheter is advanced into the right hepatic vein, where the free hepatic venous pressure (FHVP) is recorded first. Next, the balloon is inflated to occlude the hepatic vein, and the wedged hepatic venous pressure (WHVP) is measured behind the balloon (Fig. 1). In a normal liver, connections between the sinusoids will dissipate most of the "wedged pressure", the WHVP will thus reflect the sinusoidal pressure and can slightly underestimate the true portal pressure. In a cirrhotic liver, however, connections between the sinusoids are disrupted and a static column communicating with the portal vein will be created upon inflation of the balloon. Consequently, the WHVP will reflect the portal vein pressure in patients with cirrhosis.

Table 1 Pros and cons of different tools for diagnosing CSPH

+	-
Invasive portal pressure measurement	
Precise measure of portal pressure	Invasive
	Costly
	Measurement will be influenced by deep sedation and positive pressure ventilation
HVPG	
Gold standard based on abundance of available research	Only available in tertiary care centers
Can be combined with transjugular liver biopsy and/or right heart catheterization	Poor correlation in the presence of veno-venous communications
	Poor correlation in the presence of non-sinusoidal portal hypertension
	Requires fluoroscopy
EUS-PPG	
Also suited for pre- and post-sinusoidal portal hypertension	Requires EUS skill set
Can be combined with EUS evaluation (varices, liver lesions, etc.), EUS-guided liver biopsy, EUS-guided elastography and/or other endoscopic procedures	Not suited in the presence of large-volume ascites interposing the needle tract or aberrant anatomy
	Not suited in patients with severe coagulopathy
	More data needed (not known if cutoffs for HVPG can be extrapolated for EUS-PPG)
Noninvasive portal pressure assessment	
Noninvasive	No quantification of true portal pressure
Easily repeated over time	Increased liver stiffness (i.e., "false positive") outcomes can result from the presence of liver congestion, inflammation, obstructive cholestasis, steatosis or infiltrative liver disease
Ultrasound	
Ascites, SPSS and reversal of flow in the portal vein are pathognomonic for CSPH in patients with cirrhosis	Other signs are not specific for portal hypertension
Inexpensive	Operator-dependent
Widely available	
Transient elastography (TE)	
Short learning curve	Fibroscan® itself is expensive (although one-time expense)
Can be performed by trained nurses or technicians	LSM/SSM can be difficult to measure in patients with obesity, ascites and/or small spleens (although improved with the XL probe and spleen-dedicated device)
ARFI/SWE/SE	
Less expensive than TE since software can be added on ultrasound devices	Experience in conventional ultrasound required
	SE makes use of static force (i.e., manual compression or physiologic motion) and is therefore more operator-dependent
MR elastography	
Assessment of the entire liver and spleen	Expensive
	Only available in tertiary care centers
Serum markers	
Inexpensive (if non-patented)	No quantification of true portal pressure
	Should be combined, e.g., with elastography, to reach high sensitivity and/or specificity

CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; EUS-PPG, endoscopic ultrasound portal pressure gradient; EUS, endoscopic ultrasound; SPSS, spontaneous portosystemic shunts; TE, transient elastography; ARFI, acoustic radiation force impulse; SWE, shear wave elastography; SE, strain elastography; MR, magnetic resonance imaging

The difference between the two (WHVP – FHVP) constitutes the HVPG [8,18]. The concept of HVPG was established in the early 50s and was quickly accepted as the gold standard for PHT assessment [18]. Since then, an abundance of evidence has proven that a higher HVPG correlates with a greater risk of development of varices, decompensation, hepatocellular carcinoma (HCC) and mortality [5,13,14,19]. Based on HVPG measurement, patients with chronic liver disease can be stratified into 3 groups with: a) normal portal pressure (HVPG 1-5 mmHg); b) subclinical portal hypertension (6-9 mmHg); or c) CSPH (HVPG ≥10 mmHg) [1,5].

HVPG is a useful tool to assess risk and guide treatment in an individual patient. The procedure can easily be combined with a transjugular liver biopsy in patients in need of tissue diagnosis, and even with a right heart catheterization to diagnose portopulmonary hypertension [20]. The procedure is invasive, but generally considered safe, since complications (such as bleeding or arrhythmia) very rarely occur. HVPG is a valuable, albeit indirect, measure of portal tension. Unfortunately, the correlation between the WHVP and a

Table 2 Features of different tools for diagnosing CSPH

Features	HVPG	EUS-PPG	Ultrasound	TE	ARFI/SWE/SE	MRE	Serum markers
Hemodynamic information (portal pressure)			*				
Morphologic information (fibrosis grade)							
Accurate (high sensitivity and specificity)							
Noninvasive							
Inexpensive							
Efficient							
Simple							
Widely available							
Validated							

*PHT-specific sonographic features of CSPH such as portosystemic shunts, ascites and/or reversal of flow in the portal vein

GREEN = yes/YELLOW = intermediate/not always, RED = no

PHT, portal hypertension; HVPG, hepatic venous pressure gradient; EUS-PPG, endoscopic ultrasound portal pressure gradient; TE, transient elastography; ARFI, acoustic radiation force impulse; SWE, shear wave elastography; SE, strain elastography; MRE, magnetic resonance elastography

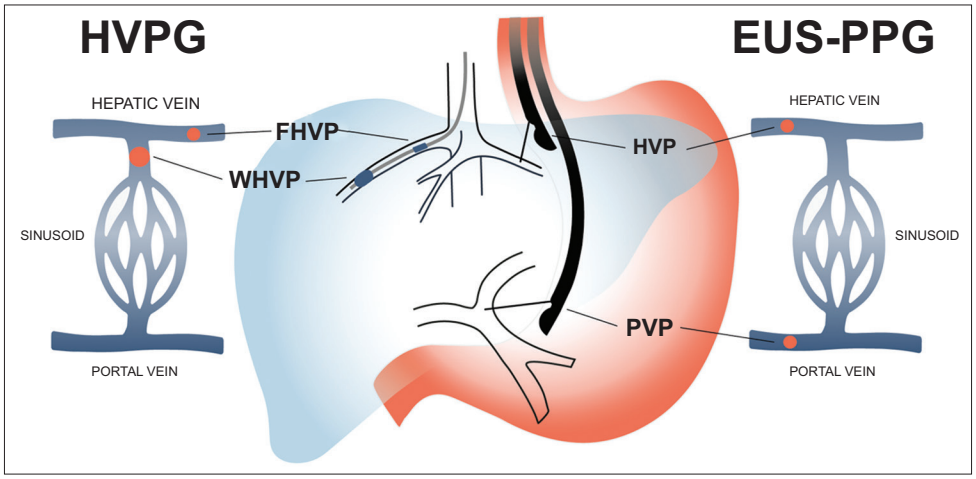

Figure 1 Comparison of the invasive indirect (HVPG) and direct (EUS-PPG) techniques for measuring portal pressure
EUS-PPG, endoscopic ultrasound portal pressure gradient; FHVP, free hepatic venous pressure; HVP, hepatic venous pressure; HVPG, hepatic venous pressure gradient; PVP, portal venous pressure; WHVP, wedged hepatic venous pressure

direct measurement of the portal vein pressure (PVP) is not perfect. In one study investigating the correlation of WHVP and direct PVP in patients with viral and alcohol-related liver disease receiving TIPS, the 2 measurements differed by more than 10% in 14% of cases [21]. Moreover, in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) cirrhosis receiving TIPS, the discrepancy was even more pronounced: disagreement was observed in 37.5% of patients, mainly because the WHVP underestimated the true PVP [21]. Along these lines, several studies have demonstrated that approximately 5-15% of MASLD patients experience decompensation even when their HVPG is below 10 mmHg—a threshold previously considered a "safe zone" for decompensation [13,22-24]. This underestimation of true portal pressure is probably due to an underlying mixed pattern of sinusoidal and pre-sinusoidal portal hypertension in MASLD, which has also been observed in patients with primary biliary cholangitis (PBC) [21,25]. With MASLD slowly becoming one of the leading causes of liver cirrhosis (worldwide prevalence of 32.4% and the second-leading cause of liver transplantation), this shortcoming of our current gold standard is important to acknowledge [3]. However, it should be mentioned that, despite these shortcomings, HVPG still holds prognostic information in patients with MASLD. A recent multicenter study showed that, in patients with compensated MASLD, those with HVPG <10 mmHg had a 9.7% rate of decompensation after 5 years compared to 30.7% of patients with CSPH [23]. Therefore, the paradigm of "the higher the HVPG, the worse the prognosis" still holds true.

An additional factor that could lead to an underestimation of portal pressure during HVPG measurements is the presence of intrahepatic veno-venous communications, which will prevent the establishment of a static column upon balloon inflation, causing the WHVP to underestimate the portal pressure [25]. Veno-venous communications have been reported in up to 35% of patients with end-stage liver

disease [26]. Moreover, HVPG measurement is invasive, costly, involves an interventional radiological skill set (which is often only accessible in tertiary centers), and requires the use of fluoroscopy. Although HVPG has laid the foundations of portal hypertensive research, it has failed in terms of practical implementation and broad dissemination in clinical practice, because of the aforementioned limitations.

The advent and expansion of the therapeutic endoscopic ultrasound (EUS) platform has introduced a possible alternative and direct route of targeting the portal vein via transgastric puncture [27]. EUS-guided portal pressure gradient (PPG) measurement was first described in a case report by Fuji-Lau *et al* in 2014, followed by the first human pilot study by Huang *et al* in 2017 [28,29]. Analogous to HVPG measurement, first the (left or middle) hepatic vein is punctured to measure the hepatic venous pressure (HVP), then the intrahepatic portal vein is punctured to measure the portal venous pressure (PVP), and subsequently they are subtracted to obtain the gradient (EUS-PPG) (Fig. 1). In a recent study, Martinez-Moreno *et al* compared EUS-PPG to HVPG in 30 patients and showed a very good correlation of 0.82 (0.65-0.91). Still, 13% showed a discrepancy of more than 5 mmHg between the 2 gradients [30]. While bleeding and infection are important concerns of the approach via the gastrointestinal tract, multiple studies so far have demonstrated the safety (0-9.6% adverse event rate) and technical success (91.7-100%) of this procedure [30-33]. To limit the risk of bleeding, the needle should always be guided through the hepatic parenchyma before puncturing the vein, allowing the liver tissue to act as a natural tamponade upon withdrawal of the needle [27]. Additionally, most authors mention the use of prophylactic antibiotics to reduce the risk of infection [30-33]. In the study of Martinez-Moreno *et al*, 2 patients developed upper gastrointestinal bleeding following EUS-PPG measurements, which might be associated with the use of a 22-G needle, instead of the FDA-approved 25-G needle [30].

EUS-PPG is particularly interesting in conditions where the HVPG might underestimate the true portal pressure (i.e., intrahepatic veno-venous communications, porto-sinusoidal vascular disease, PBC, MASLD) or when HVPG is difficult or impossible to obtain (i.e., liver vascular diseases, Budd–Chiari syndrome). In this scenario, Zhang *et al* showed an excellent correlation of 0.92 between transjugular HVPG/PPG and EUS-PPG in 11 patients with non-sinusoidal PHT [31]. The real advantage of the EUS-guided approach to portal pressure measurement is the possibility of creating a "one-stop procedure". EUS-PPG can be combined with an echo-endoscopic evaluation of the liver parenchyma and adjacent tissues to detect signs of advanced liver disease (e.g., nodular liver surface, hypertrophic caudate lobe, ascites, liver nodules, portal vein thrombosis, splenomegaly, varices or portal hypertensive gastropathy). Additionally, it provides the option of simultaneous EUS-guided liver biopsy, EUS-guided liver elastography or additional therapeutic endoscopic procedures, such as variceal band ligation, endoscopic retrograde cholangiopancreatography or endoscopic bariatric procedures [27,34]. Importantly, EUS-PPG is not recommended in patients with severe coagulopathy, or when ascites is obstructing the needle tract. Furthermore, it is yet to be confirmed if the same cutoffs as defined for HVPG (i.e., ≥10 mmHg for CSPH) can be extrapolated to EUS-PPG.

Noninvasive portal pressure assessment

The invasive nature of the previously discussed techniques has driven the search for alternative, noninvasive methods to measure portal pressure, such as conventional imaging methods, elastography and serum markers. While some of these tools may also be useful for assessing the extent and severity of liver fibrosis, this will not be the primary focus of this chapter.

Conventional imaging methods are frequently used in patients with advanced chronic liver disease (ACLD), particularly for biannual HCC surveillance. Abdominal ultrasound is a noninvasive, straightforward and cost-effective screening method for indirect signs of PHT. A few imaging findings are specific for CSPH in patients with chronic liver disease: namely, the presence of ascites, collaterals/SPSS and reversal of flow in the portal vein on Doppler imaging [35,36]. These signs are 100% specific and can diagnose CSPH without the need for invasive measurement. SPSS, for instance, are present in around 60% of patients with cirrhosis, and patients with both CSPH and SPSS have a higher risk of developing decompensating events than patients who have CSPH without SPSS (68% vs. 44%, P=0.047) [12]. Splenomegaly, portal vein dilation and reduction of portal vein flow are other suggestive, but less specific signs of CSPH that should trigger the search for the presence and potential causes of cirrhotic or non-cirrhotic PHT using other noninvasive or invasive techniques [36]. Various other ultrasound features, based on either grayscale, Doppler or contrast-enhanced ultrasound (altered portal flow velocity or Doppler patterns, portal vein diameter, hepatic vein arrival time, etc.) have been investigated as tools for estimating PHT. However, most of these methods are insufficient for quantification of PHT and, more importantly, none have found their way into clinical practice [5,37]. Additionally, ultrasound evaluation is operator-dependent and can be influenced by respiration, timing of meals, inflammation, congestion, equipment, etc. [38]. The use of computed tomography and magnetic resonance in the diagnosis of PHT has also been explored, but results are inconclusive. These imaging modalities are more suited for detailed mapping of the portal venous system, but are not recommended for stratifying the severity of portal pressure [5,37].

Elastography is a rapidly evolving diagnostic field that uses biomechanical features associated with the elastic restoring properties of deformed or displaced tissue. Tissue deformation/displacement, also called "strain", can be caused by mechanically induced pressure or acoustic pulses generating micron-level tissue movements [39,40]. In general, tissues with increased stiffness will deform or displace less. When dynamic strain (i.e., mechanical or acoustic vibration) is applied, the displacement of tissue will be propagated in both the vertical and perpendicular

horizontal plane and will generate "shear waves". The velocity of these shear waves can be quantified, and is higher in stiff tissues than in soft tissues [27,39,41]. Increased stiffness is often caused by an elevated vascular and/or interstitial pressure, which is seen in many conditions, making them detectable and quantifiable by elastography [39]. Liver stiffness correlates with the presence of fibrosis. Since fibrosis is the main determinant of PHT, especially in the earlier stages, it also correlates with portal pressure [5]. One should be aware, however, that other pathological and physiological conditions can also increase stiffness. Potential confounding factors, such as liver inflammation (including acute alcoholic steatohepatitis), obstructive cholestasis, nodular regenerative hyperplasia, liver congestion and infiltrative liver diseases, should be excluded before performing liver stiffness measurement (LSM), and patients should be fasting [39]. Furthermore, high grades of steatosis can increase liver stiffness, potentially leading to "false positive" results. Hence, liver stiffness should be interpreted carefully in patients with obesity. Nevertheless, liver stiffness is a measure with a continuous scale, and higher values increase the likelihood of CSPH, also in patients with MASLD.

Different elastography devices and software have been produced by multiple manufacturers, but in general they can be divided into 5 elastography mechanisms: strain elastography, acoustic radiation force impulse (ARFI) imaging, shear wave elastography (SWE), transient elastography (TE) and magnetic resonance elastography (MRE). Fig. 2 compares the different elastography devices and techniques. Although the main principles behind the various sonoelastography devices are similar, they do rely on different algorithms. In general, all elastography systems have excellent inter- and intraobserver agreement, and values within the normal (system-specific) range can safely exclude the presence of chronic liver disease.

TE, measured with the Fibroscan® device (Echosens, Paris, France), remains the most extensively studied elastography method for diagnosing both fibrosis and PHT [42]. The concept of cACLD, established at the Baveno VII conference, is based on an LSM of ≥10 kPa measured by TE, and reflects the continuum of severe fibrosis to cirrhosis where patients are at risk of CSPH and decompensation [25,35]. The Baveno VII guideline also endorsed the "rule of 5". Increments of 5 kPa in LSM (5-10-15-20-25 kPa) correlate with an increasing risk of fibrosis, PHT and liver-related death. CSPH can be ruled out by an LSM ≤15 kPa plus platelet count >150,000/μL and ruled in by an LSM ≥25 kPa with acceptable accuracy (sensitivity and specificity both >90%). Importantly, these rule-in criteria had not been validated in patients with MASLD and obesity, and recent studies have shown that specificity drops below the accepted 90% threshold in these patients [16,25,43].

Not only spleen size but also spleen stiffness measurement (SSM) has been shown to reflect the presence of PHT. An increased portal pressure will cause splenic outflow obstruction, leading to splenic parenchyma congestion and even fibrosis. SSM has been suggested as a more direct surrogate of portal pressure compared to LSM, since SSM is unaffected by liver congestion, cholestasis or inflammation [15,44]. CSPH can be ruled out by an SSM ≤20 kPa and ruled in by an SSM ≥40 kPa using TE with a 50 Hz probe, or ruled out with SSM ≤25 kPa and ruled in with SSM ≥55 kPa using the 100 Hz probe [16,25,43]. The 100 Hz probe has been specifically designed to measure the spleen, which has a greater intrinsic stiffness compared to the liver, and thus has greater precision for SSM [45].

LSM and SSM measured by ARFI or SWE can also diagnose CSPH, but other cutoffs should be used. In 2020, a consensus panel endorsed the "rule of 4" for LSM (5-9-13-17 kPa) for

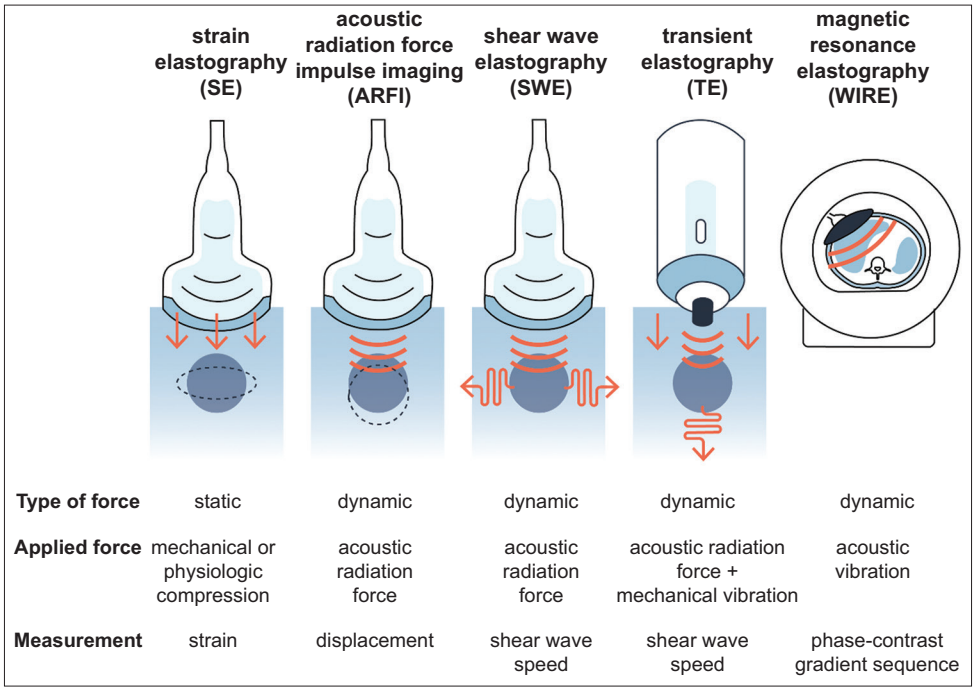

Figure 2 Comparison of different elastography devices and techniques

staging liver disease with ARFI- or SWE-based techniques, analogous to the Baveno VII rule of 5. The panel recommended an LSM value of 17 kPa or higher for ruling in CSPH, but advised confirmation with a second test [46]. No consensus statements exist regarding spleen stiffness measured by ARFI/SWE. One prospective multicenter study investigating SWE for diagnosing CSPH proposed an SSM value ≥35.6 kPa as a rule-in threshold for CSPH [47]. Both ARFI and SWE can be found incorporated into the software of ultrasound and endoscopic ultrasound devices. The availability of the B-mode ultrasound view helps select an area free of artefacts (i.e., large vessels and bile ducts, gallbladder, ligaments, ascites and other off-target tissues). The operator should therefore have experience in the use of conventional B-mode ultrasound.

MRE offers the advantage of evaluating a large volume of parenchyma (especially 3D MRE) making it less prone to sampling error. However, its use is hindered by the high costs and limited availability due to the need for specialized software, equipment (including an acoustic driver placed on the patient's upper abdomen) and expertise [35,41]. While MRE has yielded promising results regarding diagnosing fibrosis/cirrhosis, studies investigating its use in predicting CSPH (i.e., HVPG ≥10 mmHg) have reported suboptimal results (area under the curve [AUC] <0.80), for both liver and spleen stiffness [35,48-50].

Serum markers, including well-established clinical scores and experimental biomarkers, have been the original research focus for noninvasive fibrosis assessment. Some of these blood-based tests have also been studied for diagnosing CSPH. Although many serum markers correlate with the presence of signs of PHT or even HVPG, no single biomarker has demonstrated high accuracy in quantifying PHT.

It is thus clear that, to this day, the perfect noninvasive serum marker for PHT has not been found. However, the combination of certain noninvasive tests (NITs) can significantly improve diagnostic accuracy. A few tests combining serum markers, as well as elastography and/or spleen size, showed high accuracy (AUC >0.80) in diagnosing CSPH, such as the VITRO score (von Willebrand factor antigen + platelets), LSPS score (LSM by TE + spleen size + platelets), the portal hypertension risk score (LSM by TE + spleen size + platelets + sex), PSR score (platelets + spleen size), Baveno VII ± SSM model (LSM by TE + platelets ± SSM by TE 50/100 Hz), the ANTICIPATE ± NASH model (LSM by TE + platelets ± BMI) and the Non-Invasive CSPH Estimation Risk (NICER) model (LSM by TE + platelets + BMI + SSM by TE 100 Hz) [5,25,35,51-53]. The latter two have been specifically designed to accommodate the lower accuracy of elastography in obese patients. Machine learning models have additionally been used to help define the best combination of NITs to diagnose CSPH; however, their accuracy was not significantly higher compared to other noninvasive (combination) tests [54,55].

The correlation of many of the (single or combined) noninvasive tools, such as serum tests and elastography with HVPG, is high but not perfect. Therefore, the use of 2 cutoff points, one to rule out (high sensitivity) and the other to rule in (high specificity), is advisable. This consequently will lead to a "gray zone", where CSPH can neither be ruled in nor ruled out. However, the sequential application of multiple NITs can help in this regard [56]. Two recent studies, for example, showed that the addition of SSM (dual cutoff ≤20 kPa and ≥50 kPa for 50 Hz, ≤25 kPa and ≥55 kPa for 100 Hz) to the Baveno VII model reduced the gray zone from 54% to 35-38% [16,43]. Thus, combinations of NITs can and should be used to determine or exclude the presence of CSPH. See Fig. 3 for an example of an integrated algorithm using platelets, LSM and SSM (by TE). For patients remaining in the gray zone, or when a more accurate measurement of PHT is necessary, invasive methods are, however, still needed.

One for all and all for one: how do we treat CSPH?

Currently, the only available and approved chronic therapy for CSPH are non-selective beta-blockers (NSBBs) such as propranolol, nadolol and carvedilol [25]. NSBBs block beta-1 and beta-2 adrenergic receptors, which reduce heart rate and cardiac output and cause splanchnic vasoconstriction, respectively. This counteracts the compensatory hyperdynamic circulation that results from increased intrahepatic resistance in cirrhosis [10]. Since the hyperdynamic circulation typically occurs in later stages of PHT, NSBBs are effective for CSPH (i.e., HVPG ≥10 mmHg) but not for subclinical PHT (i.e., HVPG 5-10 mmHg) [1,10,59,60]. Some studies suggest that NSBBs have additional benefits in the treatment of patients with cirrhosis through non-hemodynamic properties, such as anti-inflammatory and anti-angiogenic effects, which could help reduce the progression to first or further decompensation, and even death [59,61,62]. Carvedilol is technically not a pure beta-blocker since, aside from its beta-1/2 blocking properties, it also blocks alfa-1 adrenergic receptors, which causes intrahepatic vasodilation and further decreases portal pressure. Studies have demonstrated that carvedilol achieves a greater reduction in HVPG, with more patients reaching an adequate hemodynamic response (i.e., HVPG reduction of ≥20% or to <12 mmHg) compared to propranolol [63]. Carvedilol, consequently, has taken the place of the first-line NSBB in the treatment of CSPH [25,64].

Possible and potentially important side-effects of NSBBs include bradycardia, (orthostatic) hypotension, fatigue, reduced exercise capacity, impotence, nausea and blurred vision [10]. Intolerance unfortunately leads to treatment cessation in an estimated 15-20% of patients [8,59,65]. It is also worth mentioning that caution is needed when starting NSBB in women with childbearing potential, since these drugs are best avoided during pregnancy.

Conflicting research has been published about the risk of NSBBs in patients with decompensated cirrhosis. NSBBs can be used, but caution is necessary for patients with refractory ascites, especially those with an impaired cardiac reserve, as they generally already have a low blood pressure and relative renal hypoperfusion [66,67]. Research suggests that the effect of NSBB on cardiac output and heart rate might be more pronounced in patients with decompensated cirrhosis, without resulting in greater HVPG reduction [66]. Therefore, guidelines

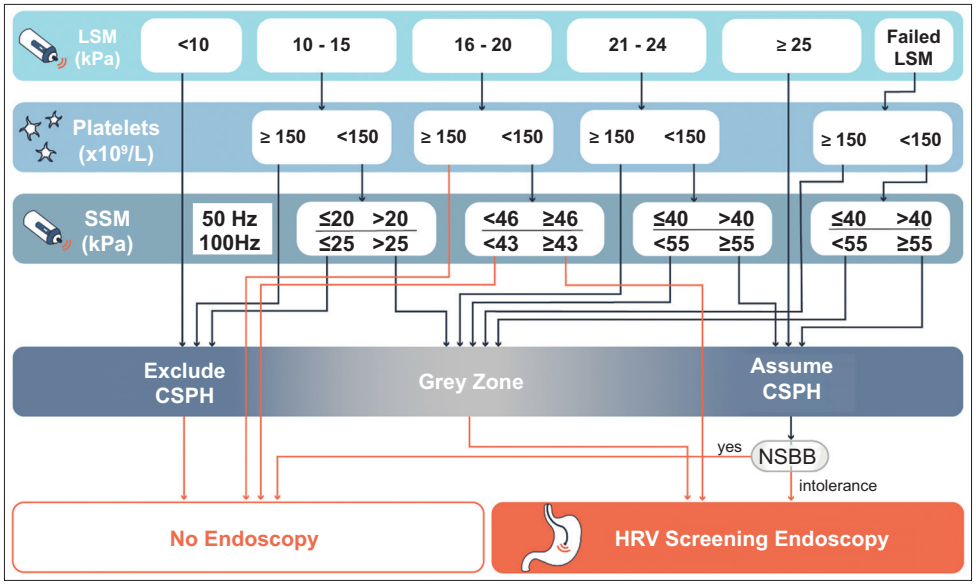

Figure 3 Example of an integration algorithm based on LSM by TE, platelets and SSM by TE for detection of CSPH and screening for HRV in patients with cACLD. Flowchart based on the following algorithms: Baveno VI criteria [25], combined Baveno VI + SSM algorithm by Colecchia *et al* [57] and Vanderschueren *et al* [58], Baveno VII criteria [25], Baveno VII + SSM criteria by Dajti *et al* [16,43] and Jachs *et al* [16]
LSM, liver stiffness measurement; TE, transient elastography; SSM, spleen stiffness measurement; CSPH, clinically significant portal hypertension; NSBB, non-selective beta-blocker; CI, contra-indication; HRV, high-risk varices; cACLD, compensated advanced chronic liver disease; TE, transient elastography

advise using propranolol instead of carvedilol in patients with refractory ascites, and temporarily stopping NSBB in patients with hypotension, hyponatremia, SBP, HRS and other forms of acute kidney injury [25,68]. The latter can be safely done for up to 6 days without causing a hemodynamic hypertensive rebound [68]. Accepted practice when starting NSBB therapy is to "start low and go slow", gradually increasing the dose to the maximally tolerated level. In general, higher doses than carvedilol 25 mg/day and propranolol 80 mg/day should not be pursued [10,64,68].

Other pharmacological treatments investigated for PHT are statins, nitrates, renin–angiotensin system (RAS)-blockers, prazosin and clonidine. Promising results have been shown for statins in the treatment of CSPH. Simvastatin can significantly reduce HVPG, especially when combined with NSBBs, and might also decrease cirrhosis progression and mortality [69-71]. Statins can induce significant side-effects, such as hepatotoxicity and rhabdomyolysis. However, these side-effects are dose-related and can be monitored; thus, starting simvastatin at a low dose is considered safe [8,70]. While larger studies are needed before statins can be recommended for treatment of CSPH, they should certainly be considered in patients with CSPH and dyslipidemia and/or high cardiovascular risk [25]. Nitrates such as isosorbide-5-mononitrate are ineffective as monotherapy, but have been shown to work synergistically with NSBBs to reduce portal pressure. RAS-blockers (captopril, enalapril, losartan, etc.) have a potential effect on CSPH, but hypotension and decreased renal function are feared side-effects, precluding use in cirrhotic patients, particularly if decompensated. Prazosin and clonidine have also been shown to have portal pressure-reducing properties, but, again, their systemic and renal side-effects preclude use in cirrhotic patients [6,8]. The latter findings underline the difficulties in finding a pharmacological agent for treating CSPH, namely inducing intrahepatic vasodilation without causing extrahepatic vasodilation. Therefore, NSBB (and carvedilol) have remained the cornerstone in the treatment of CSPH in cirrhotics for decades. Needless to say, there is an ongoing need for new, better and safer therapies.

Aside from these pharmacological treatments, we must not forget TIPS as a swift and effective alternative treatment for CSPH. TIPS insertion carries inherent risks (shunt-related hepatic encephalopathy, ischemic hepatitis, cardiac decompensation, thrombosis, etc.) and should thus always be preceded by a careful individual risk-benefit assessment. Because of its risk profile, TIPS (similar to liver transplantation) should only be considered in patients with decompensated cirrhosis, except possibly in the context of preoperative TIPS before non-hepatic abdominal surgery. For a more in-depth discussion regarding indication, contra-indication, technical considerations and other aspects of TIPS insertion, we refer to the guidelines and other reviews [25,68,72,73].

Prevention is better than cure: when and why do we treat?

In chronic liver disease, the number one priority should always be treating the underlying cause of the disease. Etiologic cure will halt or even reduce fibrogenesis in the liver, thereby stopping the rise in portal pressure [74,75]. However, many etiologies of cirrhosis, such as alcohol use disorders, metabolic

syndrome, primary sclerosing cholangitis and PBC, are challenging to treat. Additionally, the progression to cirrhosis can remain unnoticed and undiagnosed. Therefore, many patients with chronic liver disease present in the CSPH stage of the disease.

Previously, treatment of CSPH was reserved for those with high-risk varices (HRV), large gastric varices or severe portal hypertensive gastropathy for primary or secondary prophylaxis of bleeding [76]. The therapeutic window for NSBBs has opened far more since the publication of the PREDESCI trial, which showed that NSBBs reduce the risk of first decompensation in patients with CSPH. Mainly, the development of ascites was reduced from 20% to 9% with the use of NSBBs over a median follow up of 37 months [77]. A meta-analysis, including individual patient data from 352 patients, confirmed this statement by showing that carvedilol can reduce risk of decompensation (subdistribution hazard ratio [SHR] 0.51, 95% confidence interval [CI] 0.29-0.89) and mortality (SHR 0.42, 95%CI 0.19-0.90) [78]. Based on these results, the Baveno VII guideline recommended treating every patient with CSPH for prevention of first or further decompensation [25].

Caution is needed when extrapolating these results to the general chronic liver disease population. Firstly, this recommendation is based on randomized controlled trials that mainly included patients with (untreated) hepatitis C and alcohol-related cirrhosis, and excluded elderly patients and those with impaired cardiac reserve or renal impairment. Secondly, the presence of CSPH was diagnosed by HVPG. If replaced by an NIT-based diagnosis using the 90% specificity rule-in criterium, there will be a 10% chance of a false positive result. However, a recent *post hoc* study of the PREDESCI trial confirmed the ability of NITs to select candidates for NSBB treatment [79,80]. Thirdly, another PREDESCI *post hoc* analysis, as well as the previously mentioned meta-analysis, suggested that the benefit of NSBB in CSPH might be confined to those patients with varices (of any grade) [77,78]. It is thus unclear whether the benefits of NSBB therapy outweigh the potential side-effects in all patients with CSPH. Nevertheless, starting NSBB therapy in patients with CSPH makes sense from a theoretical point of view, and indeed has the potential of not only reducing the risk of first and further decompensation, but also lowering mortality and reducing the need for liver transplantation. Another benefit of NSBB therapy is that it eliminates the need for screening endoscopies, since the finding of HRV will not influence treatment in patients already on NSBBs in the setting of primary prophylaxis [25]. This is relevant since asymptomatic patients often find repeated endoscopic screenings burdensome.

In order to treat CSPH, one must first be able to diagnose CSPH. Table 3 summarizes how and when the previously discussed diagnostic tools could suggest starting NSBBs. However, the benefits of starting NSBBs should always be balanced against potential side-effects and risks, especially in the context of primary prophylaxis.

Table 3 Diagnosing CSPH using invasive and noninvasive tests

Invasive diagnostic tools	
HVPG	≥ 10 mmHg*
EUS-PPG	≥ 10 mmHg* (to be validated)
Noninvasive diagnostic tools	
Clinical	Clinical decompensation (hepatic encephalopathy, ascites, variceal bleeding)
Endoscopy	Gastroesophageal varices or variceal bleeding
	Portal hypertensive gastropathy
Ultrasound	Spontaneous portosystemic shunts
	Ascites (confirm if SAAG >1.1, ascitic proteins <2.5 g/dL)
	Reversal of flow in the portal vein
TE	LSM ≥ 25 kPa* (in patients with viral, alcohol or non-obese MASLD)
	SSM ≥ 40 kPa for 50Hz probe* SSM ≥ 55 kPa for 100Hz probe*
ARFI/SWE	LSM ≥ 17 kPa* (confirmation with a second test is advised)
	SSM ≥ 35.6 kPa* (to be validated)

*Test generates continuous values: higher values indicate higher likelihood of having CSPH

CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; EUS-PPG, endoscopic ultrasound portal pressure gradient; SAAG, serum ascites albumin gradient; TE, transient elastography; ARFI, acoustic radiation force impulse; SWE, shear wave elastography

Loosening the grip: can we ever stop NSBB therapy?

Treatment of PHT is often considered successful when the HVPG is <12 mmHg, or a reduction of at least 10% (preferably 20% in the setting of secondary prophylaxis) from baseline HVPG is reached [60,77,81,82]. Unfortunately, not every patient is responsive to NSBB treatment. Response rates vary between 20-60% for propranolol and 50-70% for carvedilol, depending on baseline HVPG, dose used, compliance, etc. [10,63,68]. In clinical practice, response to NSBB therapy is often not assessed, mainly because sequential HVPG measurement is invasive, costly and not always available, especially given the lack of alternative pharmacological therapies for non-responders. Moreover, since NSBBs also have non-hemodynamic beneficial effects, one could argue for continuing the treatment when tolerated, even in patients without a hemodynamic response. On the other hand, assessing portal pressure and treatment response does provide prognostic information.

NITs to evaluate the response to NSBB have been studied, and spleen stiffness, in particular, seems promising in this regard. Kim *et al* demonstrated that changes in SSM measured by ARFI could predict the response to carvedilol therapy as primary prophylaxis in cirrhotic patients with HRV, a finding also supported by a small study by Marasco *et al*, using a 50Hz-TE device [83,84]. SSM also appears to decrease significantly after TIPS implantation [85]. However, more data are needed before we can implement this method in clinical practice. For LSM, the Baveno VII guideline states that a decrease in LSM ≥20% associated with LSM

<20 kPa, or any decrease to an LSM <10 kPa, indicates a reduced risk of decompensation and liver-related death [25]. This recommendation is supported by a recent study by Semmler *et al*, including 2508 patients undergoing sequential LSM by TE [86].

In theory, NSBBs can be discontinued after the resolution of CSPH, which can occur after etiological treatment of the underlying liver disease. The Baveno guideline suggests that, in patients with compensated ACLD on NSBB for the prevention of first decompensation who reach complete removal or suppression of the primary etiological factor, LSM can be performed to assess presence of CSPH. If the LSM is <25 kPa, an upper gastrointestinal endoscopy should be scheduled (ideally 1-2 years after "etiological cure") and when no gastroesophageal varices are found, NSBB therapy could be stopped [25]. Important contributors to liver disease progression, such as overweight/obesity, diabetes and alcohol consumption, should ideally also be tackled [25]. Thus, the decision to discontinue NSBBs in a patient with compensated ACLD should be made on a case-by-case basis.

In patients with previously decompensated ACLD on NSBB for the prevention of further decompensation, guidelines do not provide statements regarding whether and when discontinuation of NSBBs could be considered. It is likely that these patients will first have to achieve "hepatic recompensation", which is defined as the achievement of etiological cure, sustained improvement of biochemical liver function and resolution of portal-hypertensive symptoms without the need for diuretics or prophylactic therapies [25]. However, even when hepatic recompensation is reached, data are currently lacking (though awaited) to suggest that this permits the discontinuation of NSBBs. For now, most patients on NSBB for secondary prophylaxis of portal hypertensive symptoms will probably continue this therapy for life, unless transplanted or receiving TIPS.

Concluding remarks

CSPH is the main driver of decompensation and liver-related death in chronic liver disease. Accurate diagnosis and timely treatment are essential, though challenging, especially in patients with significant but not clinically evident PHT. NSBBs prevent decompensation in compensated patients and reduce death and the need for liver transplantation in decompensated patients. However, until now they remain the only approved therapy for PHT, despite uncertainties around treatment effect and discontinuation. While HVPG ≥10 mmHg is the diagnostic gold standard, its limitations have led to the rise of promising noninvasive tools, particularly elastography. These advances support better risk stratification and individualized care, with continued research offering hope for improved outcomes in patients with CSPH.

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