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Elastography for the Evaluation of Portal Hypertension

Roxana Șirli, Iulia Rațiu and Ioan Sporea

Abstract

Liver cirrhosis, regardless of its etiology, is an important health problem with a chronic evolution, characterized by the possibility of developing several important complications. The best management of these patients implies the correct and early diagnosis of the disease and of its complications. A major complication of cirrhosis is portal hypertension. The reference method for its diagnosis is the direct measurement of hepatic vein portal gradient, an invasive procedure. In the last years, several noninvasive techniques for the evaluation of liver fibrosis were developed, such as biological tests and elastographic methods. Ultrasound-based and MRI-based elastographic techniques have been assessed as predictive tools for the presence and severity of portal hypertension. This paper reviews published data regarding the value of ultrasound and MRI-based elastography (liver, spleen, or both) for the evaluation of portal hypertension.

Keywords: portal hypertension, clinically significant portal hypertension (CSPH), elastography, liver stiffness, spleen stiffness

1. Introduction

The prevalence of chronic hepatopathies in daily practice is increasing due to their multiple causes, such as chronic viral infections, alcoholic or non-alcoholic steatohepatitis, cholestatic or autoimmune chronic liver disease. Evaluation of such patients is important for therapeutical decisions, follow-up, and for prognosis assessment.

One main complication of advanced chronic liver disease is portal hypertension (PHT), and the exact evaluation of this entity is crucial for further steps. The direct measurement of hepatic vein portal gradient (HVPG) is the “gold standard” for portal hypertension assessment, but this procedure is invasive, and it is not available in all centers of hepatology. Upper endoscopy for the evaluation of possible esophageal varices or portal gastropathy is a surrogate used in daily practice. Ultrasound and other imaging methods that can reveal collateral circulation in the abdomen can be used to suggest portal hypertension.

Elastography techniques developed in the last 10–15 years mainly evaluate liver stiffness as a marker of fibrosis severity and, lately of portal hypertension. More recently, spleen stiffness was used for the assessment of liver disease severity and evaluation of portal hypertension. Ultrasound-based elastography techniques are the most used in practice, but some studies also evaluated magnetic resonance elastography (MR-E).

2. Portal hypertension: definition and standard method of diagnosis

The main consequence of fibrosis during chronic liver disease, regardless of the etiology, is a perturbation of the sinusoidal blood flow in the liver that leads to increased pressure in the portal venous system, namely portal hypertension (PHT). Additionally, as a compensatory reaction, splanchnic vasodilatation further aggravates the PHT, this mechanism contributing 25–30% to the portal vein pressure [1].

The standard method to diagnose PHT is by measurement of the hepatic venous pressure gradient (HVPG). It is an invasive method that implies catheterization with a balloon catheter of one of the hepatic veins, via the jugular or via a cubital vein. The balloon catheter, with a pressure transducer at the tip, is inflated as to totally occlude the hepatic outflow, thus measuring the wedge hepatic venous pressure (WHVP) [2]. With the balloon deflated free hepatic venous pressure (FHVP) is measured. The hepatic venous pressure gradient (HVPG) is calculated as the difference between WHVP and FHVP [3].

Normal values of HVPG are ≤ 5 mmHg. As liver injury and fibrosis progress, the HVPG increases progressively. HVPG between 5 and 10 mmHg represents subclinical PHT while HVPG ≥ 10 mmHg represents the threshold from where PHT-related complications may occur and thus is known as clinically significant PHT (CSPH) [3, 4].

Upper endoscopy is the standard diagnostic method for the presence and severity of esophageal varices (EV), the most visible and severe consequence of PHT. To diagnose clinically significant EV (large-grade 2, or 3 EV), a screening program with periodic upper digestive endoscopy should be implemented. However, it is an invasive procedure and numerous endoscopies are performed in patients with advanced liver disease without finding EV, thus raising questions regarding cost-efficiency and patients' acceptance.

Considering the invasiveness of these methods, their availability, and also patients' acceptance, effective noninvasive methods are needed to assess the presence and progression of PHT, as well as the occurrence of EV and their bleeding risk [5].

3. Ultrasound-based elastographic techniques in the liver

According to international guidelines [6, 7], elastography techniques can be classified into Strain Elastography (used mostly for breast, thyroid, and prostate) and Shear Waves Elastography (SWE). In SWE, an external impulse generates shear waves inside the examined organ. The shear waves speed is subsequently measured by ultrasound. Based on the type of external impulse and measurement technique of the shear-waves speed, SWE elastography is subdivided into Transient Elastography (mechanic external impulse); Point SWE (pSWE)—in which an Acoustic Radiation Force Impulse (ARFI) is used as stimulus and the shear-waves speed is measured in a point; and real-time elastography which includes 2D-SWE and 3D-SWE (ARFI used as a stimulus, the shear-waves speed is measured in an area of interest and, in the same time, a color-coded elastogram is generated) [6, 7]. It must be noted that cut-off values proposed for various stages of fibrosis are system-specific.

3.1 Transient elastography (TE)

Transient Elastography was the first elastographic method developed for the evaluation of liver stiffness (LS) [8] and it is not integrated into a standard ultrasound system. It uses a FibroScan device (Echosens, Paris, France) that includes a

special ultrasound probe (3.5 MHz for the standard M probe) integrated into a piston that “punches” the body surface. The “punch” generates shear waves that propagate into the liver. Their velocity is measured by pulse-echo ultrasound acquisition and is proportional to LS, increasing in parallel with LS. Increased BMI decreases the feasibility, an inconvenience partially solved by using an XL probe. The FibroScan device displays Young’s modulus, expressed in kilopascals (kPa), which is proportional to the shear-wave velocity [6, 7, 9, 10].

Several published meta-analyses have demonstrated that LS measurement by TE is a reliable method for diagnosing cirrhosis, with a pooled sensitivity ranging from 84.4 to 87% and a pooled specificity ranging from 91 to 94.69% [11, 12]. Liver stiffness measured by TE showed a good correlation with HVPg and the presence of EV; as a result, it has been evaluated as a noninvasive tool for portal hypertension quantification. The first studies were performed in rather small numbers of patients. In an Italian study, the AUROC for predicting HVPg ≥ 10 mmHg was 0.99 with 97% sensitivity (Se), while for predicting HVPg ≥ 12 mmHg the calculated AUROC was 0.92 with 94% Se. The calculated cut-offs were 13.6 kPa for HVPg ≥ 10 mmHg and 17.6 kPa for HVPg ≥ 12 mmHg. The cut-off for predicting any EV was 17.6 kPa (AUROC 0.76, Se-90%) [13]. In a French study, TE predicted HVPg ≥ 10 mmHg with AUROC 0.945 (cut-off 21 kPa) [14]. In a study that followed up 100 patients for 2 years, none of the patients who initially had LS measurements (LSM) values < 21.1 kPa (the calculated cut-off) had PHT complications, vs. 47.5% of those with higher values [15].

Finally, a method’s value is demonstrated by meta-analyses. Regarding TE and portal hypertension, a meta-analysis that included 18 studies with more than 3500 patients was published in 2013 [16]. The conclusion was that, due to the low specificity of this method, TE cannot replace upper gastrointestinal endoscopy for EV screening. However, in 2017 another meta-analysis on 11 studies was published [17]. The summary correlation coefficient was 0.783. Summary Se, Sp, and area under the hierarchical summary receiver operating characteristic curve (AUC) were 87.5%, 85.3%, and 0.9 respectively. In summary, LS correlated well with HVPg and had a good diagnostic performance in diagnosing CSPH. Low cut-off values of 13.6–18 kPa were proposed to ensure a good sensitivity for screening purposes.

The latest EASL guidelines on noninvasive tests for the evaluation of liver disease severity and prognosis proposed an algorithm for risk stratification in compensated advanced chronic liver disease (cACLD) using the Baveno VI criteria [4, 18]: patients with LSM < 20 kPa and PLT $> 150 \times 10^9/L$ should be considered to have a very low risk of having CSPH. These criteria [4] have been well validated for the identification of patients with cACLD who are unlikely to have varices needing treatment and can safely avoid variceal screening endoscopy, while those not meeting these criteria are at an increased risk of clinical decompensation. Numerous studies validated these criteria [19–23]. However, in the latest update of the EASL and AASLD guidelines on noninvasive tests for liver fibrosis severity, no clear recommendation was given on whether 20 kPa or 25 kPa is better to rule in the risk of clinical decompensation [18, 24]. A very recently published study demonstrated that patients not meeting the Baveno VI criteria were indeed at a significantly higher risk of liver decompensation. More importantly, the patients with LSMs ranging from 20 to 25 kPa, regardless of the platelet count, might be classified as having a medium risk of clinical decompensation, while those with LSM higher than 25 kPa could be classified as having a high risk of clinical decompensation [25].

In a meta-analysis performed exclusively in patients with chronic viral hepatitis, it was suggested that two cut-offs can be used, namely, ≤ 13.6 kPa to rule out CSPH

(pooled Se 96%), and ≥ 22 kPa to rule in CSPH (pooled Sp 94%), thus confirming Baveno VI consensus recommendations [26]. Another systematic review and meta-analysis of 30 studies, including 8469 participants, assessed the accuracy of Baveno VI criteria (LSM <20 kPa and platelet count $>150 \times 10^9$ cells/L) and Expanded Baveno criteria (LSM <25 kPa and platelet count $>110 \times 10^9$ cells/L) to identify high-risk varices (HRVs) in patients with cACLD were published in 2019 [27]. This meta-analysis concluded that the Baveno criteria and expanded criteria can identify patients with HRVs with high sensitivity but with low specificity. The Expanded Baveno criteria reduce the proportion of unnecessary endoscopies, with a higher rate of missed HRVs [27].

3.2 Shear-wave elastography techniques using acoustic radiation force impulse (ARFI)

In this type of elastography, the shear waves are generated into the tissue by acoustic impulses. It is divided into point Shear-Waves elastography (pSWE) and real-time elastography (2D-SWE and 3D-SWE).

3.2.1 Point shear-waves elastography (pSWE)

In pSWE, the shear-waves speed is measured in a small, fixed-size region of interest (ROI), at the focal point of the US beam, the results being expressed either in m/s, or converted into kPa [6, 7]. pSWE technology is used by several vendors, using proprietary techniques implemented on standard US machines. The first one that appeared on the market and was studied the most is Virtual Touch Tissue Quantification (VTQ) by Siemens, followed by ElastPQ from Philips, and later by techniques by Hitachi, Esaote, Samsung, and others.

Several studies demonstrated the value of VTQ elastography to predict cirrhosis when compared to liver biopsy, the cut-offs ranging from 1.55 to 2 m/s and AUROCS ranging from 0.89 to 0.937 [28, 29], with similar performance to TE in diagnosing cirrhosis [30, 31]. These results were confirmed by several meta-analyses [32–34].

Regarding VTQ measurements as a predictor of PHT, the published studies had shown controversial results. In European studies, VTQ had poor results in predicting large EV, with AUROCs 0.596 [35] and 0.580 [36]. A Japanese study had shown much better results: for a cut-off of 2.05 m/s, VTQ had 83% Se, 76% Sp, and an AUROC of 0.89 to predict any grade EV; while a cut-off of 2.39 m/s had 81% Se, 82% Sp and an AUROC of 0.868 to predict HRVs [37].

3.2.2 Real-time shear-wave elastography (2D-SWE and 3D-SWE)

Two-dimensional Shear-Wave Elastography (2D-SWE) also uses Acoustic Radiation Force Impulse technology (ARFI) to generate shear waves into the tissue. As opposed to pSWE, in 2D-SWE multiple ARFI impulses evaluate a large field of view, inside which a ROI can be selected. Thus, tissue elasticity is displayed in a “real-time” color map (elastogram) superimposed on a B-mode image (red for stiff tissues and blue for soft ones), and also a numerical value is displayed. LS measured in the user-adjustable ROI is expressed in kPa or m/s at the operator’s decision [6, 7]. 2D-SWE technology is used by several vendors, using proprietary techniques implemented on standard US machines. The first 2D-SWE that appeared on the market was developed

by SuperSonic Imagine and integrated into the Aixplorer™ system, followed by other vendors (General Electric, Canon/Toshiba, Philips, Samsung, etc.).

Liver 2D-SWE has proven to be an accurate method for diagnosing cirrhosis, with AUROCs ranging from 0.94 to 0.98, for cut-off values ranging from 10.4 to 11.7 kPa (lower than those of TE) [38–42].

There are promising results regarding the predictive value of 2D-SWE for predicting CSPH. Studies evaluating 2D-SWE from Supersonic Imagine (2D-SWE.SSI) reported cut-offs of 15.2 kPa to predict CSPH, with AUROC 0.819 (85.7% Se and 80% Sp) and 15.4 kPa [43], with AUROC 0.948 (Se and Sp > 90%) [44]. Similar good results have been obtained using 2D-SWE from General Electric (2D-SWE.GE) [45].

An individual patient data meta-analysis was published in 2020 regarding the performance of 2D-SWE.SSI to identify CSPH, severe PHT, and large varices in cirrhotic patients, using HVPg and upper endoscopy as reference. The study included data of 519 patients from seven centers. A cut-off of 2D-SWE.SSI < 14 kPa ruled out CSPH with 85% accuracy (summary AUROC (sROC)—0.88, 91% Se and 37% Sp) [46]. 2D-SWE.SSI ≥ 32 kPa ruled in CSPH with 55% accuracy (sROC—0.83, 47% Se, 89% Sp). The authors concluded that LS values by 2D-SWE.SSI below 14 kPa may be used to rule out SCPH, however, 2D-SWE.SSI cannot predict varices needing treatment [46].

The consensus panel on Ultrasound Liver Elastography of the Society of Radiologists proposes a vendor-neutral “rule of four” (5, 9, 13, 17 kPa) regarding LSM by ARFI techniques (pSWE and 2D-SWE) for viral etiologies and NAFLD: LS ≤ 5 kPa (1.3 m/sec) has a high probability of being normal; LS ≤ 9 kPa (1.7 m/sec), in the absence of clinical signs, rules out cACLD; values between 9 kPa (1.7 m/sec) and 13 kPa (2.1 m/sec) are suggestive of cACLD but need further tests for confirmation; LS ≥ 13 kPa (2.1 m/sec) are highly suggestive of cACLD. There is a probability of CSPH with LS ≥ 17 kPa (2.4 m/sec) [47].

4. Ultrasound-based elastographic techniques in the spleen

Portal hypertension leads to splenic congestion, which induces architectural changes in the splenic arteries and veins, resulting in fibrosis and an increase in spleen stiffness (SS). Recently, noninvasive techniques that measure spleen stiffness to identify CSPH are gaining more and more interest [48, 49]. SS can be evaluated through elastography techniques, such as TE and ARFI based technologies (pSWE and 2D-SWE) [6, 7, 50, 51].

4.1 Transient elastography

Since TE is the oldest ultrasound-based elastographic technique, it was the first used to assess SS as a predictor of PHT, based on the idea that splenomegaly is one of the clinical signs of cirrhosis. Several studies found a good correlation between SS and LS by TE in patients with cirrhosis and between SS and the presence of EV or HVPg.

The first study that evaluated SS measurement (SSM) by TE showed that SS values become higher as the liver disease is more advanced, correlating well with LS, the association being stronger ($r = 0.587$) in patients with varices [52]. The SS value was also higher in patients with EV, the best cut-off to predict the presence of EV was ≥46.4 kPa (AUROC = 0.781, PPV = 93.4%). If LS and SS are combined, using LSM ≥ 19 kPa for high Se and SSM ≥ 55 kPa for high Sp, the diagnostic accuracy

increased to 88.5%. In an Italian study on 100 patients with HCV cirrhosis, SS correlated better with HVPG than LS ($r^2 = 0.78$ vs. $r^2 = 0.7$) [53]. For the same specificity, SS has a better sensitivity than LS to rule in the presence of EV and both HVPG >10 mmHg and HVPG >12 mmHg).

In another study on 498 patients, the authors developed a prediction model combining SS with Baveno VI criteria, useful to rule out HRVs, that could make it possible to avoid a significantly larger number of unnecessary upper endoscopies as compared to Baveno VI criteria only. Applying the newly identified SSM cut-off (≤ 46 kPa) to exclude HRVs, or Baveno VI criteria, 35.8 and 21.7% of patients in the internal validation cohort could have avoided upper digestive endoscopy, with only 2% of HRVs being missed with either model. By combining SSM with Baveno VI criteria an additional 22.5% endoscopies could be avoided, reaching a final value of 43.8% spared EGDs, with $<5\%$ missed HRVs [54]. Results were confirmed in a prospective external validation cohort, as the combined Baveno VI and SSM ≤ 46 kPa model would have safely spared 37.4% endoscopies, as compared to 16.5% when using the Baveno VI criteria alone, with 0 HRVs missed [54].

Initial studies regarding SSM were made using the standard FibroScan® device (SSM@50 Hz), with a ceiling threshold of 75 kPa, which could lead to underestimating EV severity. Therefore, EchoSens developed a novel spleen dedicated FibroScan® (SSM@100 Hz), in which the vibrator has a higher frequency (100 Hz) than the standard machine (50 Hz). In a study comparing the two techniques, Stefanescu et al. found out that valid measurements could be obtained in a significantly higher proportion by patients by SSM@100 Hz than by SSM@50 Hz (92.5% vs. 76.0%, $p < 0.001$) [55]. The accuracy of SSM@100 Hz to predict the presence of EV (AUC = 0.728) and HRVs (AUC = 0.756) was higher than that of other noninvasive tests, including LSM. The proportion of spared endoscopies using Baveno VI criteria (8.1%) significantly increased if combined with SSM@50 Hz (26.5%) or SSM@100 Hz (38.9%, $p < 0.001$ vs. others). The proportions of missed HRVs were 0% for Baveno VI criteria and 4.7% for combinations [55].

4.2 Shear-wave elastography techniques using acoustic radiation force impulse (ARFI)

4.2.1 Point shear-waves elastography

There are several studies that evaluated VTQ for the assessment of SS, alone [35, 56, 57] or in comparison with TE [58]. Studies considering HVPG as a reference for evaluating SSM performance revealed a remarkable accuracy of SSM in predicting CSPH [59, 60]. A study published in 2019 found out that VTQ is an excellent method of predicting HRVs. Patients with EV of any grade had significantly higher average SS values as compared to those without EVs (3.37 m/s vs. 2.79 m/s, $p < 0.001$), while patients with HRVs had even higher SS values (3.96 m/s vs. 2.93 m/s, $p < 0.001$) [61].

4.2.2 Real time shear-wave Elastography

A prospective multicentric study evaluated LS and SS by 2D-SWE.SSI as predictor of CSPH considering HVPG as a reference in 158 subjects, with valid measurements obtained in 109 patients [62]. $LS > 29.5$ kPa and $SS > 35.6$ kPa were able to “rule-in” CSPH, with a specificity $>92\%$. $LS \leq 16.0$ kPa and $SS \leq 21.7$ kPa were able to “rule-out” CSPH. Patients with a $LS > 38.0$ kPa had a substantial risk of having CSPH. In

patients with $LS \leq 38.0$ kPa, a $SS > 27.9$ kPa ruled in CSPH. This algorithm has 89.2% Se and 91.4% Sp to rule-in CSPH [62].

A recent study evaluated SSM by 2D-SWE.GE to predict the presence of HRVs and compared it to VTQ (a pSWE technique). The optimal SS cut-off value by 2D-SWE was 13.2 kPa (AUROC=0.84), while for VTQ it was 2.91 m/s (AUROC=0.90), with no significant performance difference between the two techniques ($p = 0.1606$) [63].

A meta-analysis published in 2016, including 12 studies (5 regarding SSM by TE, 5 SSM by pSWE, and 2 SSM by strain elastography) evaluated SS as a predictor of the presence of EV. SS detected the presence of any EV with 78% Se, 76% Sp, 3.4 positive likelihood ratio (LR), 0.2 negative LR, and a diagnostic odds ratio (DOR) of 19.3 [64]. In a subsequent meta-analysis of nine studies, SS predicted the presence HRVs with 81% Se, 66% Sp, 2.5 positive LR, 0.2 negative LR, and 12.6 DOR [64].

A meta-analysis published in 2018, including 9 studies (3 regarding SSM by TE, 2 SSM by pSWE, and 4 SSM by 2D-SWE) showed a good correlation between SS and HVPG, the summary correlation coefficient was 0.72 [65]. In detection of CSPH, the sensitivity, specificity, AUC and DOR were: 88%, 84%, 0.92 and 38 respectively; while for severe PHT they were 92%, 79%, 0.79 and 41 respectively [65].

5. Magnetic resonance elastography (MRE)

The predictive value of MRE for liver fibrosis severity was evaluated by several meta-analyses, which found diagnostic accuracies higher than 90% for the diagnosis of advanced fibrosis and cirrhosis [66–68]. Among its advantages are that it is evaluating the whole liver at the same time, the possibility of steatosis quantification and also of possible focal liver lesions, as well as the fact that the presence of obesity does not decrease feasibility or accuracy [18]. The main limitations of MRE include its prohibitive costs, limited availability, and the need for specialized infrastructure, equipment, and considerable need for radiological expertise.

A preliminary study on 34 patients regarding the value of liver MRE to predict PHT evaluated by HVPG showed a significant but weak correlation of LS with HVPG ($r = 0.478$, $p = 0.016$). ROC analysis provided significant AUROCs for LS to predict PHT (0.809), and CSPH (0.742) [69]. In another study on 263 patients, LS and SS by MRE were evaluated as predictors of the presence of EV. SS was higher in patients with EV and, in multivariate analysis, there was a significant association of SS with EV, but not of LS and EV. The AUROC of MRE-SS for EV was 0.853. A cut-off value of 9.53 kPa had 84.4% Se and 73.7% Sp to predict EV [70]. Similar satisfactory results have been obtained by two other studies [71, 72].

In a recently published meta-analysis, LS and SS by MRE were evaluated as predictors of PHT. Fourteen studies were included (12 evaluating LS and 8 evaluating SS). The pooled and weighted Se, Sp, and AUROC for LS were 83%, 80% and 0.88 respectively, while for SS they were 79%, 90% and 0.92 respectively [73]. The conclusion of this meta-analysis was that SS may be more specific and accurate than LS for detecting PHT.

6. Conclusions

Numerous studies on the diagnostic performance of elastography-based methods to predict the presence of CSPH have been published, mostly reporting data on liver

and spleen stiffness measurements by means of TE, pSWE, and 2D-SWE, which represent promising tools for portal hypertension screening.

According to international guidelines, patients with NASH cirrhosis and those with viral etiology who have LS by TE ≥ 20 –25 kPa should be considered at elevated risk of having endoscopic signs of PH. Patients with LS by TE < 20 kPa and with a platelet count $> 150 \times 10^9$ cells/L have a very low risk of having varices requiring treatment and can avoid screening endoscopy.

Patients with LS values evaluated by pSWE and 2D-SWE higher than 17 kPa (2.4 m/sec) are likely to have CSPH.

Spleen stiffness using TE, pSWE or 2D-SWE can be used for PH evaluation.

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