ULTRASOUND ELASTOGRAPHY IN CHRONIC VIRAL HEPATITIS – A REVIEW

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ABSTRACT

Assessing liver fibrosis is essential for the management of chronic viral hepatitis. Over the last ten years we have been witnessing the emergence of many noninvasive methods tending to replace liver biopsy for the purpose of staging the fibrosis. There are two main classes of noninvasive methods that have demonstrated a fair ability to classify fibrosis compared to liver biopsy: the biochemical/hematological markers (also known as serologic markers) and the imaging techniques. Among the imaging techniques, ultrasound elastography has had an explosive development, with many different approaches, based on different physical principles, trying to achieve the same goal: the measurement of the stiffness of a tissue or organ. Transient elastography (TE), acoustic radiation force impulse imaging (ARFI) and shear-wave elastography (SWE) are the major players of the moment. Transient elastography is the oldest of the methods; it is validated by numerous independent studies and is already recommended by some of the main professional hepatology associations as a possible replacement for liver biopsy for the assessment of the fibrosis in chronic C hepatitis. ARFI and SWE have also been analyzed in many studies that showed their value as noninvasive liver fibrosis evaluation methods. Data abounds in the literature; the techniques are evolving so fast that even experienced ultrasonographers have trouble integrating all the information. This review is an attempt to summarize the most important data on the subject of ultrasound elastography in chronic viral hepatitis.

Keywords: liver elastography, chronic hepatitis, liver fibrosis, noninvasive, transient elastography, ARFI, shear wave elastography

CORE TIP

Liver ultrasound elastography is one of the most recent acquisitions in the field of medical imaging. There are many approaches in liver elastography, based on different physical principles, but the goal remains one: the evaluation of the liver elasticity, and thus the assessment of the stage of liver fibrosis. Three main techniques are now subjects for numerous researches: transient elastography, acoustic radiation force impulse imaging and shear-wave elastography. The purpose of this review is to summarize and organize the up-to-date information available on the subject of liver ultrasound elastography in chronic viral hepatitis.

INTRODUCTION

The medical exploration of the liver started long time ago with palpation. This was the first method used to obtain information about the liver and permitted our medical predecessors to evaluate its size, shape, position, sensitiveness and hardness. Palpation is mentioned as a diagnostic method in the Edwin Smith Surgical Papyrus, in 1600s BC (1). With the recent acquisitions in the medical imaging field, the physical characteristics of the liver can be more precisely evaluated and even quantified.

Ultrasonography was introduced in medical practice in the late 1940s and became widely avail-

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able in the 1960s. Since then the technique evolved becoming more and more sensitive and refined and many ultrasound based imaging techniques and expansions of the original method emerged. Doppler ultrasonography, one of the first expansions is already implemented on most machines. Over the last 15 years, two new techniques were introduced in medical practice: in 2002 Contrast Enhanced Ultrasound (CEUS) and in 2003 ultrasound elastography.

The use of ultrasound elastography in medical practice started with transient elastography (Fibroscan®), but few years after its implementation, as large studies already proved the value of this method for staging liver disease, numerous other methods have been developed. Among these, ARFI (Acoustic Radiation Force Impulse Elastography), Real Time Elastography and Shear Wave Elastography are here, used already in practice and subject of many studies aiming to establish their usefulness in the management of chronic liver diseases. The development of elastography is different from that of earlier expansions of the ultrasonography, with many approaches, different techniques using different physical methods trying to achieve the same goal: the measurement of the elasticity of a tissue or organ. Most of these techniques were introduced over the very last years and even experienced clinical ultrasonographers are having problems putting all the new information together and extracting the essence of the techniques in order to improve their overall management of the examined patients.

The main idea of using elastography is that any pathological process that involves a tissue modifies its elasticity. The identification of the affected tissues and even the quantification of their stiffness can be very useful in making a correct diagnosis and staging of a disease, thus allowing a better management of the patient.

In the following pages we will be trying to synthesize the information available on the use of elastography in the management of the patients with chronic viral hepatitis.

THE PHYSICS OF ULTRASOUND

Understanding basic ultrasound physics is essential for any clinician that performs ultrasonography.

Ultrasound machines generate ultrasound waves and receive their reflected echoes. Ultrasounds are mechanical waves with frequencies outside the human audible spectrum, ranging from 18 KHz to 150 MHz. In medical ultrasound, the frequencies used are between 1 MHz to 10 MHz, the ones in the lower part of the interval having a good penetration, but providing a poor resolution, while those found in the highest part of the interval provide a good resolution with less penetration (2).

The ultrasounds are produced using the piezoelectric effect. This effect is specific to some materials, best-known being the quartz crystal. The piezoelectric effect consists in the occurrence of an electrical potential difference between the two surfaces of a piezoelectric material subjected to a mechanical deformation. The phenomenon can take place also in the opposite sense: a quartz crystal subjected to a potential difference will suffer a mechanical deformation. This deformation is followed by a friction in the crystal's inner structure, which generates ultrasounds (2).

Brightness mode (B mode) also known as 2D mode is the basic mode that is most commonly used (3). Using this mode we obtain a 2D slice in grayscale of an anatomical region. The tones of gray represent basically the translation into images of the different impedances of the tissues in the examined plan. B-mode transducers generate the ultrasound and receive the reflected echoes at the same time.

The same piezoelectric crystal emits ultrasounds and then receives (listens) ultrasound echoes. Actually over 99% of the time is spent "listening". The emission/reception cycle is repeated million times per second. The principle is called "pulsed-echo". Returning sound waves are converted into images through a complex analysis algorithm performed by the ultrasound machine's computer and displayed on the monitor as a 2D grayscale imagine (4).

Although in a pathological lesion the tissue stiffness is modified, classic ultrasound imaging may not capture this fact. The extent of a lesion may not be correctly evaluated by simple ultrasonography. Moreover, in diffuse liver diseases, like chronic viral hepatitis or even cirrhosis; although fibrosis modifies the stiffness of the tissue, the aspect on classic ultrasound can be normal. Tissue elasticity and echogenicity are generally uncorrelated (5).

Other imaging modes are *M-mode* (motion mode) which captures returning echoes in a single line of the B-mode image and displays them on a time axis and *Doppler mode,* which is used to analyze the characteristics of direction and speed of tissue motion and blood flow.

THE PHYSICS OF ELASTOGRAPHY

Elasticity is the physical property of materials to return to their original shape after the removal of

the force that caused the deformation. The mechanical properties sensed by palpation and measured by elastography are associated with the elastic restoring forces in the tissue that act against a type of deformation (shape change) known as shear.

Two types of shear can be described (1):

1. The "simple shear" refers to the shear resulting from applying a force that displaces a single location in the region of interest. The volume of the so compressed object does not change, only its shape.

2. The "pure shear" results from a compressive force applied to displace the whole surface of the body – the same object will be compressed axially, resulting in a lateral expansion that conserves volume.

Shear waves are transverse waves that occur in an elastic medium when it is subjected to periodic shear.

Although processes in real elastography are more complex, acoustic radiation force can be approximated by "simple shear" while compression elastography can be approximated by "pure shear".

Basically, the ultrasound elastography involves applying a force on the examined area and then measuring the reaction of the tissue to that stress. There are numerous approaches for the applied force and for the measurement, as well as for data processing and display of the tissue response.

The characterization of the elasticity of a region of interest is currently done by two methods:

- By assessing the relative displacement caused by a static or dynamic deformation – qualitative and relative assessment
- By measuring the shear wave's propagation velocity through the analyzed tissue – quantitative assessment.

Displacement or strain imaging methods are based on the fact that various tissues have different elasticity. When subjected to similar forces, tissues with higher elastic modulus deform less, as compared to tissues with lower elastic modules. The technique involves achieving images before and after compression and analyzing them comparatively based on various complex algorithms. The result is an elastogram, a map of relative stiffness in a region of interest. These methods offer qualitative information.

The forces applied on the tissue can be quasi-static (active external displacement of tissue surface by transducer manual vibration or passive –cardiovascular or respiratory movements, or muscular contraction) or dynamic (ultrasound induced – focused acoustic radiation force impulse at depth).

Methods based on shear wave speed measurement are based on the fact that shear waves have different speed of propagation through tissues with different stiffness. These methods result in a quantitative evaluation of the stiffness of the region of interest.

Biological environments allow propagation of two types of waves: longitudinal and shearing. For longitudinal waves, the direction of particles oscillation is the same as the propagation direction of the wave front. For the shear waves, the oscillation of the particles occurs perpendicularly to the direction of propagation.

The shear waves can be mechanically induced (as in transient elastography) or ultrasound induced (acoustic radiation force impulse).

Variants of elastography that not only measure and give average numeric results, but also represent on a map the stiffness from a region of interest have been developed recently. These are commercially available as Virtual Touch IQ (Siemens) and Shear-Wave ElastographyTM/SWE (Supersonic Imagine).

STRAIN ELASTOGRAPHY

Recently, most of the important manufacturers have included in their high-end devices strain elastography optional modules. This technique tends to become part of the routine examination especially for the superficial organs like breast or thyroid and for the prostate. Strain imaging is also available for the liver. The most extensively used in this field is the one from Hitachi (Hitachi Real Time Elastography – HI RTE) which has the largest number of studies.

HI RTE uses freehand compression of the tissues with the ultrasound transducer. Using an autocorrelation method, the system produces a real time imagine of the relative tissue elasticity, which is displayed as a 2D color-coded map. The examination of the liver is performed with the patient in supine position with the right arm elevated above the head or placed under the head, in the right lobe, placing the transducer in the space between the ribs and applying a slight pressure (7). Recently, passive internal compression of the liver from the cardiac activity has been implemented in HI RTE (5).

There have been attempts to transform this qualitative method into a semi-quantitative score, as the one in the group led by Mireen Friedrich-Rust (8), who established the German Elasticity Score. They calculated the value of the elasticity distribution for each pixel on a scale from 0 to 1 (0 = maximum

elasticity, 1 = minimum elasticity) from the color-coded map image with a program specially created for this purpose. They used statistical methods and obtained an elasticity score. The study included 79 patients and 20 controls. All 79 patients with chronic hepatitis B and C (13/66) underwent liver biopsy. Their elasticity score showed a good correlation with the result of the liver biopsy, with AUROC of 0.75 for the diagnosis of significant fibrosis ($F \geq F2$), 0.73 for the diagnosis of severe fibrosis ($F \geq F3$), and 0.69 for the diagnosis of cirrhosis ($F = F4$).

Another attempt to calculate an elasticity score based on strain imaging came from the Japanese group of Tatsumi (9), who analyzed data from 125 patients (102 with HCV, 3 with HBV and 20 non-B, non-C). They coded the pixels with values from 0 to 255 according to their color and calculated the percentage of blue area in the examined region. The so obtained score showed a negative correlation with fibrotic stage and Fibroscan findings, suggesting that real-time tissue elastography is a better test than Fibroscan with fewer limitations.

Another Japanese group conducted by Fujimoto(10) recruited 310 patients with chronic C hepatitis and analyzed their data obtaining the Liver Fibrosis Index (LFI) which was calculated from image features of RTE images, using multiple regression analysis. The correlation coefficient obtained between the LFI and the stage of hepatic fibrosis was $r = 0.68$ and significant differences exist between all stages of fibrosis ($p < 0.001$).

All of the above studies were performed with freehand compression technique and with analysis software specially created for each study. Over the last years Hitachi improved their systems by implementing passive compression and automated software for the analysis of RT imagines features.

With this system, Wang et al (11) performed a study on 55 HBV patients and 20 healthy volunteers. They analyzed the correlation between the elasticity index and the liver fibrosis stage as well as the accuracy of real-time elastography for liver fibrosis staging. The Spearman's correlation coefficient between the elasticity index and the histological fibrosis stage was 0.81 ($p < 0.001$). The areas under receiver operating characteristic curves indicating diagnostic accuracy were 0.93 ($F \geq F1$, $p < 0.001$) for the diagnosis of liver fibrosis, 0.92 ($F \geq F2$, $p < 0.001$), 0.84 ($F \geq F3$, $p < 0.05$) and 0.66 ($F = F4$, $p > 0.05$), respectively.

Using the same system, in a more recent study, the group conducted by Hu evaluated the utility of the elastic ratio (a new parameter computed by the recently introduced software module) calculated using real-time tissue elastography for assessing liver fibrosis in patients with chronic hepatitis B. They had 96 chronic hepatitis B patients enrolled in the study. They found that the elastic ratio was significantly correlated with histological fibrosis stage ($r = 0.873$, $p < 0.001$). Cut-off values were 2.62 for stage 2 and over ($S \geq 2$), 3.20 for stage 3 and over, and 3.86 for stage 4, respectively. The elastic ratio measurements had good reproducibility: 0.838 for intra-observer reliability and 0.805 for inter-observer reliability, respectively ($p < 0.001$).

However, the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) considers that the evidence with this approach is still too limited to allow recommendation for its clinical use, at least in European patients (6).

Strain elastography may play a role in the identification and characterization of focal liver masses that can occur as a consequence of chronic viral hepatitis, but currently only a small number of studies have been published on this subject (13-16).

TRANSIENT ELASTOGRAPHY (TE) (FIBROSCAN®)

The first ultrasound based elastography technique measures the velocity of a mechanically generated shear wave through the tissue and it calculates the stiffness of the liver based on this. The Fibroscan® is a dedicated machine composed of a computer and a special probe that acts as an emitter and also as a receiver of ultrasounds which is mounted on a mechanical vibrator that generates a low frequency (50 Hz) shear wave (17). The displacements induced in the medium by the shear wave are read by radiofrequency, then computed using an autocorrelation method, and derived versus depth in order to provide a strain rate image called elastogram. The analysis of this elastogram gives the velocity of the shear wave and based on this, the machine calculates the elasticity of the tissue and displays the result in kPa (KiloPascals).

Being the "oldest" of the elastographic methods, Fibroscan has already a lot of clinical data to confirm its utility in the field of hepatology. A search on PubMed with the terms "transient elastography" and "hepatitis" returns 433 results. The producer of Fibroscan counts on his site over 750 articles and over 1000 poster or oral presentations on the subject.

TE in chronic hepatitis C (CHC)

The first use and validation of transient elastography was in chronic hepatitis C. In one of the first

studies (18) the authors evaluated the intra- and inter-operator reproducibility of the method on 106 CHC patients. They found that the measurements were reproducible (standardized coefficient of variation of 3%), operator-independent and well correlated (partial correlation coefficient = 0.71, $p < 0.0001$) to fibrosis grade.

The correlation of the results of the Fibroscan with the results of the liver biopsy was assessed in many studies. I a prospective study conducted by Ziol et al (19) on 327 CHC patients they found a very good correlation of the liver stiffness measurement (LSM) with the fibrosis stage (Kendall correlation coefficient: 0.55; $P < .0001$). The areas under ROC curves were 0.79 (95% CI, 0.73-0.84) for $F \geq 2$, 0.91 (0.87-0.96) for $F \geq 3$, and 0.97 (0.93-1) for $F = 4$; for larger biopsies, these values were, respectively, 0.81, 0.95, and 0.99.

One of the first studies to establish the cut-off values of LSM for each METAVIR fibrosis stage was the one conducted by Castera in 2005 (20). The team studied 183 patients with CHC and they found the following cut-offs: 7.1 kPa for $F \geq 2$, 9.5 kPa for $F \geq 3$, and 12.5 kPa for $F = 4$ to have the best sensitivity and specificity. The areas under the receiver operating characteristic (ROC) were 0.83 for $F \geq 2$, 0.90 for $F \geq 3$ and 0.95 for $F = 4$.

Another proposed approach was to find the cut-offs that best differentiate between F0/F1 and $F \geq 2$. The study conducted by Beaugrand (21) on 494 CHC patients found 7.5 kPa to be the best trade-off between sensitivity and specificity for this purpose.

The most interesting data can be extracted from meta-analyses. The one in 2007 by Talwalkar (22) finds a pooled estimate for sensitivity of 83% (95% CI = 77%-88%) for significant fibrosis, and a pooled estimate for specificity of 83% (95% CI = 77%-88%). For the diagnosis of cirrhosis by TE, the pooled estimate for sensitivity was 98% (95% CI = 90%-100%), and the pooled estimate for specificity was 84% (95% CI = 80%-88%).

The meta-analysis conducted by Friedrich-Rust (23) included 50 studies and found the mean AUROC for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis to be of 0.84 (95% CI = 0.82-0.86), 0.89 (95% CI = 0.88-0.91), and 0.94 (95% CI = 0.93-0.95), respectively.

A meta-analysis which included 40 studies (24) found that summary sensitivity and specificity was 0.79 (95% CI 0.74-0.82) and 0.78 (95% CI 0.72-0.83) for F2 stage and 0.83 (95% CI 0.79-0.86) and 0.89 (95% CI 0.87-0.91) for cirrhosis.

Studies show that TE is not accurate enough to distinguish between contiguous stages of fibrosis, but can differentiate absence and mild fibrosis from significant fibrosis and cirrhosis, which is more critical for decisions regarding treatment (6, 22-24).

Some factors have been found to interfere with the quality of the LSM, with the accuracy of the results, among which obesity, tight intercostal spaces, liver inflammation and liver steatosis are most frequently evoked (25-27).

Based on the existent data, EASL stated that LSM can be used (especially when associated with validate biomarkers) for the assessment of the severity of the liver damage in CHC (28).

There are studies that suggest that TE could be used for the monitoring of the results of the antiviral treatment in CHC (29,30). In the study conducted by Hezode, the team followed 91 patients for 24 weeks after treatment and they found a significant decrease in liver stiffness only in patients with sustained viral response. The other study, stretched over 4 years had similar results.

The study by Masuzaki et al (31) showed an association between LSM and the risk of HCC development in patients with hepatitis Cand concluded that the utility of LSM is not limited to being a surrogate for liver biopsy but can also be applied as an indicator for the risk of HCC development. They showed that patients with higher LSM were at a significantly higher risk, with a hazard ratio, as compared to LSM less or equal to 10 kPa, of 16.7 when LSM 10.1-15 kPa, 20.9 when LSM 15.1-20 kPa, 25.6 when LSM 20.1-25 kPa and 45.5 when LSM >25 kPa.

TE in chronic hepatitis B

A study published in 2012 (32) compared the performance of TE in the two main etiologies of chronic viral hepatitis: B and C. The study team found that the overall diagnostic accuracy of TE in the CHB group was comparable to the one observed in CHC patients (AUROCs 0.867 ± 0.026 vs. 0.868 ± 0.019 for predicting $F \geq 2$, $P = 0.975$; 0.902 ± 0.029 vs. 0.894 ± 0.020 for $F \geq 3$, $P = 0.820$ and 0.935 ± 0.024 vs. 0.947 ± 0.027 for F4, $P = 0.740$ respectively). There were 202 HBV patients and 363 HCV included in this study.

Another study comparing the two etiologies was performed by Sporea et al (33). They found a significant direct correlation between LSM and fibrosis in HCV patients ($r = 0.578$, $P < 0.0001$) and also in HBV patients ($r = 0.408$, $P < 0.0001$). The correlation was more significant in HCV than in HBV patients ($Z = 2.210$, $P = 0.0271$).

Another study (34) conducted by Marcellin included 202 patients with CHB and analyzed the data of 173 of them. The statistical analysis showed that LSM was significantly ($P < 0.001$) correlated with METAVIR ($r = 0.65$) and Ishak fibrosis stage ($r = 0.65$). The AUROCs were 0.81 (95% confidence intervals, 0.73-0.86) for $F \geq 2$, 0.93 (0.88-0.96) for $F \geq 3$ and 0.93 (0.82-0.98) for $F = 4$. Optimal LSM cut-off values were 7.2 and 18.2 kPa.

Chon and his team (35) put together 18 studies comprising 2772 patients in a meta-analysis and they found out that the mean AUROCs for the diagnosis of significant fibrosis (F2), severe fibrosis (F3), and cirrhosis (F4) were 0.859, 0.887 and 0.929 respectively. The estimated cutoff for F2 was 7.9 (range, 6.1-11.8) kPa, with a sensitivity of 74.3% and specificity of 78.3%. For F3, the cutoff value was determined to be 8.8 (range, 8.1-9.7) kPa, with a sensitivity of 74.0% and specificity of 63.8%. The cutoff value for F4 was 11.7 (range, 7.3-17.5) kPa, with a sensitivity of 84.6% and specificity of 81.5%.

A particularity of chronic VHB infection is the possible occurrence of flares, which is equivalent with an increase in inflammation and is known to increase the stiffness of the liver. This is the reason why Chan proposed alanineaminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B (36). Different LSM cutoff values and algorithms were derived in this study for normal and elevated ALT levels.

A study by Jung evaluated the usefulness of TE for stratifying patients with CHB for developing hepatocarcinoma (HCC) (37). Their analysis showed that LSM could be a useful predictor of HCC development in CHB as patients with a higher LSM (> 8 kPa) were at a significantly greater risk of HCC development, with the following hazard ratios: 3.07 ($P = 0.047$) for LSM 8.1-13 kPa; 4.68 ($P = 0.012$) for LSM 13.1-18 kPa; 5.55 ($P = 0.009$) for LSM 18.1-23 kPa; and 6.60 ($P = 0.004$) for LSM > 23 kPa.

In a recent study, Kim et al assessed the clinical usefulness of TE in monitoring the treatment of CHB patients with oral antiviral agents (nucleoside and nucleotide analogues). Long-term oral antiviral therapy resulted in the improvement of liver stiffness in a substantial portion of patients with CHB (38).

ACOUSTIC RADIATION FORCE IMPULSE (ARFI) ELASTOGRAPHY

The technique we analyzed in this chapter is called **Virtual Touch™ Quantification** and was integrated several years ago by Siemens as an optional module on their high-end machines. Using this elastographic method, the operator can select a region of interest in the liver tissue visualized in B mode and this region will be mechanically excited using short duration acoustic pulses to generate localized tissue displacements. These displacements generate shear waves which propagate perpendicularly on the initial pulse. The machine then tracks the shear waves and measures their speed of propagation through the tissue and displays the value in m/s. As stiffness increases, the propagation of the shear waves becomes faster thus reflecting a more advanced fibrosis.

The method being introduced only recently, the available data is not as large as in TE case, but evidences regarding its usefulness in the management of chronic viral hepatitis are already available.

One of the first published articles came from Lupsor et al (39) and prospectively compared ARFI with TE in 112 patients with CHC that underwent liver biopsy. The results of this study suggest that ARFI has a similar performance for the diagnostic of severe fibrosis ($F \geq 3$) or cirrhosis (AUROCs of 0.86 vs. 0.92 and 0.91 vs. 0.94), respectively, while for the diagnostic of significant fibrosis ($F \geq 2$) TE performs better (AUROC of 0.94 vs. 0.85). They also tried to establish cut-off values for each fibrosis stage. The values they found to have the best sensitivity + specificity sum are: 1.19 m/s ($F \geq 1$), 1.34 m/s ($F \geq 2$), 1.61 m/s ($F \geq 3$) and 2.00 m/s (F4).

Another study that included both CHB and CHC patients established cut-off values for ARFI of 1.37 m/s, 1.45 m/s and 1.75 m/s for $F \geq 2$, $F \geq 3$ and $F = 4$ with sensitivities and specificities of 68.5% and 92.6%, 83.9% and 86%, 81.8% and 91.5% respectively (40).

A meta-analysis conducted by Friedrich-Rust included 8 studies published until October 2010, with a total of 518 patients. The mean diagnostic accuracy of ARFI AUROC was 0.87 for the diagnosis $F \geq 2$, 0.91 for the diagnosis of $F \geq 3$), and 0.93 for the diagnosis of cirrhosis (41). A more recent meta-analysis (42) containing 36 studies and 3951 patients (from 2007 to 2012) found a mean diagnostic accuracy of ARFI expressed as the AUROC of 0.84 for significant fibrosis ($F \geq 2$), 0.89 for severe fibrosis ($F \geq 3$) and 0.91 for the diagnosis of liver cirrhosis. This study also revealed te existence of heterogeneity between the different underlying liver diseases for $F \geq 3$ and $F = 4$. Finally, the last meta-analysis listed in pub-med on this subject, which was actually a comparison between Magnetic Resonance Elastography (MRE) and ARFI

found AUROCs for ARFI staging of 0.82, 0.85, 0.94, and 0.94 for F1-F4, but although the accuracy of ARFI was good, especially for higher ranks of fibrosis, the overall conclusion of this study is that MRE was more accurate than ARFI (43).

As in the case of TE, factors that may influence ARFI diagnostic accuracy were identified. In a study on 106 CHC patients, Bota et al found that female sex ($p = 0.004$), interquartile range interval ((IQR) $\geq 30\%$) $p = 0.04$), high ALT ($p = 0.008$) and high AST levels ($p = 0.003$) were associated with discordances (44). The team of Popescu, in a different study found that food intake can also influence the concordance of ARFI results with liver histological staging (45). Cholestasis is another factor that significantly increases liver stiffness assessed by ARFI as a group conducted by Pfeifer found in a study published in 2014 (46).

ARFI may also be useful in the prediction of some complications of chronic viral hepatitis, as Morishita et al showed in a study (47) on 135 patients with HCV related cirrhosis who underwent esophagogastroduodenoscopy and ARFI. The conclusion of this study was that liver stiffness measurement by ARFI is useful in predicting the presence of esophageal varices or high-risk esophageal varices in this group of patients. The team led by Takuma studied whether spleen stiffness (SS) measured by ARFI can identify patients who have esophageal varices (48). They suggested that SS could be used to identify patients with esophageal varices and found that the value of over 3.18 m/s has a 98.4% negative predictive value and 98.5% sensitivity. This study included 340 patients with cirrhosis who were subjected to ARFI and esophagogastroduodenoscopy (48).

Data regarding the use of ARFI in monitoring the results of antiviral treatment are rare. One study was performed on 98 patients with CHC who had completed antiviral treatment at least 6 months prior the inclusion in the study and then received ARFI VTTQ, TE and laboratory evaluation (49). The authors compared the group of patients with sustained viral response (SVR) with the group of patients that did not accomplish SVR.

Another study conducted by Goertz (50) included 38 patients (16 with CHB and 22 with CHC). They performed an initial ARFI evaluation of all of the patients and a second one at a mean of 2.3 years after the baseline evaluation. The analysis of the data suggested that in the group of patients with favorable response to treatment, there was a significant change in the liver stiffness (1.55 ± 0.60 m/s (baseline evaluation) versus 1.34 ± 0.47 m/s (second evaluation); $p < 0.05$) while in the patients that did not respond to treatment or received no treatment, there was an increase of the stiffness, but without statistical significance (1.57 ± 0.70 m/s versus 1.93 ± 0.77 m/s).

Liver stiffness measurement failure by ARFI seems lower than in TE's case as Cassinotto and his team showed in a recent study, with failure rates of 11.2% with the M probe and 2.3% with the XL probe for TE, and 0% with ARFI elastography. Still, unreliable results with ARFI were frequent in the case of obese or overweight patients (Body mass index (BMI) over 30 kg/m^2) – 48.8% vs. 14.5% in the case of patients with BMI below 30 kg/ m^2 (51).

SHEARWAVE™ ELASTOGRAPHY (SWE)

The technique, available on the Aixplorer® system (SuperSonic Imagine, France) is the newest of the ultrasound based elastographic techniques showing promising results for the evaluation of liver fibrosis.

The history of this revolutionary technique began more than 30 years ago, when Bruneel et al published their work on the "ultrafast ultrasonic tomograph" (52). At that time it all remained in theory because the technology available did not permit putting it into practice.

ShearWave™ Elastography (SWE) is based on the measurement of the shear waves propagation speed in soft tissue. The ultrasound probe generates targeted radiation forces in the tissue to create the shear waves. Using SonicTouch™ technology, ultrasound beams are successively focused at different depths in tissues. The result is a "Mach cone" shape propagation of the shear waves, thus increasing their amplitude and improving their propagation distance (53). Instead of transmitting focused beams, which scan the whole region of interest line-per-line, ultrafast imaging is obtained by transmitting plane (unfocused or flat) waves which scan in a single transmit event over the whole region of interest (54). The progression of the shear waves is captured by the very rapid acquisition of ultrasound images (up to 20,000 images per second), called UltraFast™ Imaging. The speed of the shear waves is in the order of 1 to 10 m/s (corresponding to tissue elasticity from 1 to 300 kPa). The acquisition takes only a few milliseconds and therefore the movements of the patient or of the probe do not influence the measurements. The machine then compares consecutive frames and creates a real-time two dimensional map of the speeds of the

shear waves through different parts of the region of interest. Elasticity is displayed using a color coded image superimposed on a B-mode image, each pixel's color resulting from the calculation of Young's modulus knowing the speed of shear waves in that area. The color scale is quantitative with values expressed in kPa.

One of the earliest articles found on the subject dates from 2011 and is the result of a study conducted by Bavu et al (55). The authors enrolled 113 patients with CHC and tested SWE against TE in predicting the liver fibrosis stage diagnosed by liver biopsy. They found a good correlation ($r = 0.829$) between the elasticity measured with SWE and TE, although a mean offset of 2.40 kPa was observed between the two techniques. The AUROCs for elasticity values assessed by SSI were 0.948, 0.962 and 0.968 for patients with predicted fibrosis levels $F \geq 2$, $F \geq 3$ and $F = 4$, respectively while for TE this study revealed AUROCs of 0.846, 0.857 and 0.940, respectively. The comparison shows an advantage of SWE especially in the cases with mild and intermediate fibrosis – concluded the authors (56).

Another study also on CHC patients, conducted by Ferraioli et al (57), that included 138 consecutive patients compared SWE with TE in the assessment of liver fibrosis taking liver biopsy as a standard. They found AUROCs of 0.92, 0.98 and 0.98 for SWE and 0.84, 0.96 and 0.96 for TE in the prediction of $F \geq 2$, $F \geq 3$ and $F = 4$.

The study conducted by Leung, this time in CHB patients (56) included 226 CHB patients (with liver biopsy) and 171 healthy volunteers. The AUROCs for SWE of liver and TE of liver were, respectively, 0.86, 0.80 for $F \geq 1$; 0.88, 0.78, for $F \geq 2$; 0.93, 0.83 for $F \geq 3$ and 0.98, 0.92 for cirrhosis.

In a very recent study, published on-line in May 2014, the team of Cassinotto included 349 patients with various chronic liver diseases (hepatitis C, B, mixed hepatitis, ASH, NASH, hemochromatosis, drug-induced liver injury, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, post-liver transplantation viral reactivation and even unexplained chronic cytolysis) (58). SWE, Fibroscan, and ARFI correlated significantly with histological fibrosis score ($r = 0.79$, $p < .00001$; $r = 0.70$, $p < .00001$; $r = 0.64$, $p < .00001$, respectively). AUROCs of SWE, Fibroscan, and ARFI were 0.89, 0.86 and 0.84 for the diagnosis of mild fibrosis; 0.88, 0.84, and 0.81 for the diagnosis of significant fibrosis; 0.93, 0.87, and 0.89, for the diagnosis of severe fibrosis; 0.93, 0.90, and 0.90 for the diagnosis of cirrhosis, respectively. This study suggests that SWE has a similar performance to TE and ARFI for mild fibrosis and cirrhosis but that it could provide a more accurate staging of the severe fibrosis than TE ($p = 0.0016$) and the significant fibrosis as compared to ARFI (0.0003) (58).

All of the above studies highlighted the very low rate of failure of SWE technique especially when compared to TE. Another important aspect regarding SWE is that this technique can be applied during an ultrasonography of the liver and it can also show the heterogenic disposition of fibrosis in the liver.

CONCLUSIONS

Assessing the severity of liver disease is essential during the initial evaluation of a chronic viral hepatitis, but also in the follow-up period (with or without specific antiviral therapy). Liver biopsy is certainly the method that still brings the most complete and accurate information regarding the stage and cause of a liver disease. But it is not perfect and has disadvantages that are well known as they are repeatedly reminded in almost every article focused on noninvasive alternative methods. This is why alternative or complementary methods are needed.

Ultrasound elastography is a very important achievement of the last years development of medical imaging technology. It makes us able to "see" elasticity and quantify stiffness. And this is important because it helps us see beyond conventional ultrasonography and it improves the quality of the diagnostic and the management of the patient.

Strain elastography has limited data to sustain its use in the evaluation of the severity of the liver damage in chronic hepatitis, but with the recent technological innovations and improvements it may gain a role in this area in the future, especially in the identification and characterization of focal liver masses.

Transient elastography (Fibroscan®) is the oldest and most validated of the methods used for the quantification of liver fibrosis. Its performances and extensive independent validation have convinced the experts and now it is recommended both by the European Association for the Study of the Liver (EASL) and Asian Pacific Association for the Study of the Liver (APASL) guidelines for management of CHC as an alternative for liver biopsy (LB) in selected cases (28,60). For CHB both EASL and APASL mention TE as a possible alternative to LB (59,61). The American Association for the Study of the Liver Diseases (AASLD) does not yet recommend elastography in the guidelines for the

TABLE 1. *The performances of the ultrasound elastography techniques*

Method	Study	Etiology	No. of patients	AUROC for F ≥ 2	AUROC for F4
Strain elastography	Friedrich-Rust M. et al, 2007(8)	CHB + CHC	79	0.75	0.69
	Wang et al (11)	CHB	55	0.92	0.66
TE	Ziol et al, 2005 (19)	CHC	327	0.79	0.97
	Castera et al, 2005(20)	CHC	183	0.83	0.95
	Friedrich-Rust M. et al, 2008 (23)	CHC	MA	0.84	0.94
	Cardoso A.C., 2012 (32)	CHC	363	0.86	0.94
	Cardoso A.C., 2012 (32)	CHB	202	0.86	0.93
	Marcellin et al, 2009 (34)	CHB	173	0.81	0.93
	Chon et al, 2012 (35)	CHB	MA	0.85	0.92
ARFI	Lupsor et al, 2009 (39)	CHC	112	0.85	0.91
	Friedrich-Rust M. et al, 2011 (41)	CHB + CHC	MA	0.87	0.93
	Nierhoff J et al, 2013 (42)	CHB + CHC	MA	0.84	0.91
SWE	Bavu et al, 2011 (55)	CHC	113	0.94	0.96
	Ferraioli et al, 2012 (56)	CHC	138	0.92	0.98
	Leung et al, 2013 (57)	CHB	226	0.88	0.98
	Casinotto et al, 2014 (58)	Various	349	0.88	0.93

management of the CHB or CHC (62,63). As seen from the above presented studies, TE is useful for staging the disease, for monitoring the progression (or regression) of liver fibrosis in untreated or treated patients. All studies show that it has a poor ability to distinguish between low grades of fibrosis, but is very accurate in diagnosing severe fibrosis and cirrhosis. The performance of TE is fair in differentiating between significant ($F \geq 2$) and insignificant ($F < 2$) fibrosis. It is also proven that TE has a value in establishing a prognosis and assessing the possible complications of hepatitis. The performances of Fibroscan are influenced by several factors, but knowing them and interpreting the results in the clinical context can enhance the diagnostic value of the method. The cost of the method is still high, although lower than in the case of the liver biopsy, but with the upcoming promising competition we hope that it will decrease over time.

Acoustic Radiation Force Impulse (VTTQTM) is a relatively new technique with promising results, a reliable alternative to liver biopsy and even to TE for the purpose of staging liver fibrosis in chronic hepatitis. Studies show that ARFI has a similar performance as TE for the detection of severe fibrosis and cirrhosis. It seems also appropriate for monitoring the evolution of fibrosis in treated or untreated CHB or CHC patients and it may be a good prognostic factor for the known complications of the chronic hepatitis. It has the advantage over TE that it can be performed on the same machine as conventional ultrasonography and the region of interest can be visualized and selected by the operator. The technique is available on S2000 or S3000 from Siemens.

ShearWaveTM Elastography (SWETM) is the most recently introduced ultrasound elastography technique and it comes with innovations in the domain. This promising technique is based on UltraFast™ Imaging which makes it different from other available methods. The studies published on liver fibrosis evaluation with SWE are very favorable to this method, showing it has better results in the prediction of fibrosis stages than its main competitors, TE and ARFI even in the lower registry of absent or minimal fibrosis. But the amount of data is too small for the moment and further studies are needed to confirm these conclusions. It also seems to have a lower rate of failure than TE and can be performed during a conventional ultrasound exam. The technique is available on Aixplorer® from Supersonic.

The performances of all the methods described above are centralized in Table 1.

Transient elastography, Acoustic Radiation Force Impulse and ShearWaveTM Elastography have already established their place in the management of CHB and CHC. Their usefulness is beyond doubt and in the future they should become part of routine evaluation of patients with chronic viral hepatitis.

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