Review

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Liver Elastography – An Update

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Abstract

Liver fibrosis evaluation is very important for treatment and prognosis in patients with chronic liver disease. The "gold-standard" method for liver fibrosis assessment is still considered to be the liver biopsy, but in the last years non-invasive methods have increasingly been used, especially ultrasound based elastographic ones. The oldest and the only validated elastographic method for non-invasive liver fibrosis evaluation is Transient Elastography (TE). In the last 2-3 years, similar results to TE for liver fibrosis assessment were obtained by using Acoustic Radiation Force Impulse (ARFI) Elastography. More recently, Real Time Shear Wave Elastography (SWE) was developed and promising results were obtained by this technique. Strain elastography is less used in clinical practice for non-invasive liver fibrosis assessment. TE is also useful for predicting liver cirrhosis complications, especially portal hypertension. ARFI elastography seems to be inferior to TE in this field.

Keywords: liver fibrosis, Transient Elastography, Acoustic Radiation Force Impulse elastography, Real Time Shear Wave Elastography, strain elastography

Introduction

Chronic liver diseases are quite frequent in daily practice, either secondary to chronic infection with hepatitis viruses C or B, or with other etiologies, such as ethanol abuse (alcoholic steatohepatitis – ASH) or non-alcoholic steatohepatitis – NASH. Other chronic hepatopathies, such as autoimmune hepatitis or primary biliary cirrhosis (PBC) are also often diagnosed in daily hepatological practice.

A correct evaluation of the liver fibrosis is very important for treatment (especially for viral etiology), prognosis assessment, and long term follow-up. Liver biopsy (LB) is still considered the „gold-standard" for liver fibrosis evaluation [1], and it can also evaluate the grading of the liver diseases. Also, LB can reveal fatty infiltration or specific markers for some hepatic diseases (such as the Mallory bodies in alcoholic steatohepatitis).

A problem of LB is that the specimen obtained represents roughly only 1/50,000 of the total liver volume. Also it is a known fact that fibrosis is unevenly distributed throughout the liver. Another important problem is the relevance of the specimen obtained by LB, in terms of its dimension and the number of portal tracts. Also, it should not be forgotten that LB is an invasive method which can have complications. In a systematic review performed some years ago [2], it was demonstrated that major and minor complications occur during the procedure in up to 6% of cases, while 0.04 to 0.11% of them can be life threatening.

Thus, considering these limitations of LB in daily practice, non-invasive methods for the evaluation of liver disease severity represent an alternative. There are some authors in favor of biological markers, others in favor of elastographic methods [3,4]; while others consider that the combination of these methods can reduce the number of liver biopsies [5,6].

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Elastographic methods using ultrasound waves for the evaluation of liver fibrosis can be divided into [7]:

1. Strain Elastography (or quasi-static elastography) Hi-RT-E

2. Shear waves Elastography:

a) Transient Elastography (FibroScan);

b) "Point" shear waves Elastography – Acoustic Radiation Force Impulse (ARFI) quantification (Siemens, Phillips);

c) Real-Time Shear Waves Elastography – [Supersonic Imagine, Aixplorer system].

Due to the body of scientific evidence [8], we shall start our review with Transient Elastography, as hundreds of papers have been published on TE.

I. Transient Elastography

Technique

Transient Elastography (TE) (FibroScan, Echosens, Paris, France) uses an external actuator to produce low-frequency vibrations with frequencies in the 50-500 Hz range [9]. The solution used in the FibroScan device combines the actuator and the ultrasonic transducer in the same probe [10-12]. Induced shear waves propagate through the tissue and produce its elastic deformation. Displacement is reflected in the variation of the acquired echo signals. The ultrasonic transducer is used in pulse-echo mode to measure displacements induced into the medium by the propagation of low frequency shear waves. Both longitudinal and shear waves are generated by the same probe and the ultrasonic beam is focused by the actuator axis. The assumption of homogeneity and symmetry considerations shows that displacement on the transducer axis is purely longitudinal. Diffraction effects from the transducer result in a longitudinally polarized shear wave on the axis of symmetry. The ultrasonic beam tracks its propagation [13].

In each patient 10 valid TE measurements must be performed under fasting conditions, in supine position, by intercostal approach, with the right arm in maximum abduction. Reliable measurements were defined as: median value of 10 valid liver stiffness (LS) measurements with a success rate (SR = ratio of the number of successful acquisitions divided by the total number of acquisitions) $\geq$ 60% and an interquartile range interval (IQR=the difference between the 75th and 25th percentile, essentially the range of the middle 50% of the data) <30%.

Clinical applications

TE assessment of LS was used initially for the evaluation of chronic hepatitis C. Later, research proved the method's value in other chronic hepatopathies, such as chronic hepatitis B, hemochromatosis, primary PBC, human immunodeficiency virus (HIV)/chronic hepatitis C co-infection, or NASH.

In ***chronic hepatitis C*** patients, if the LS is greater than 6.8–7.6 kPa (according to the results of several studies and meta-analysis) [3,5,14], there is a great probability of finding significant fibrosis on liver biopsy (F$\geq$2) and subsequently the patient requires antiviral therapy. Probably, in such cases, LB is not required for a treatment decision. The cut-off values for predicting liver cirrhosis (F=4) range between 11.8 – 13.3 kPa [5,15,16].

Regarding the use of TE in ***chronic hepatitis B*** patients, Marcellin et al [17] evaluated liver fibrosis in 202 patients by means of LB and TE. LS was significantly ($p<0.001$) correlated with histological fibrosis ($r=0.65$). The AUROCs for F$\geq$2, F$\geq$3 and F=4 were 0.81, 0.93 and 0.93 respectively. Optimal LS cut-off values were 7.2 and 11.0 kPa for F$\geq$2 and F=4, respectively, by maximizing the sum of sensitivity and specificity, and 7.2 and 18.2 kPa by maximizing the diagnosis accuracy.

Some studies tried to compare the performance of TE for liver fibrosis evaluation in patients with chronic hepatitis B and C. In a study from our group [18], 140 patients with chronic hepatitis B and 317 patients with chronic hepatitis C were evaluated by means of LB and TE. The correlation with fibrosis was significantly higher in patients with chronic hepatitis C: $r=0.578$, vs. $r=0.408$, $p=0.02$. The mean values of LS assessed by TE were similar for each stage of fibrosis in patients with chronic hepatitis B and C. Afterwards, Cardoso et al [19] who evaluated 202 patients with chronic hepatitis B and 363 subjects with chronic hepatitis C, revealed that TE exhibited comparable accuracies, sensitivities, specificities, predictive values and likelihood ratios in hepatitis B and C patients. Contrary to studies in the Asian population [20], ALT levels did not influence LS cut-off values for predicting various stages of liver fibrosis.

In order to minimize the risk of overestimating fibrosis during ALT flares in patients with chronic hepatitis B, Chan et al [20] presented LS cut-off values for various stages of fibrosis according to the aminotransferases levels: for predicting severe fibrosis (F $\geq$ 2) – 9 kPa in patients with normal ALT and 12 kPa in patients with ALT higher than 5 times the upper limit of normal; and for predicting liver cirrhosis (F =4) – 12 kPa in patients with normal ALT and 13.4 kPa in those with high ALT.

The studies published until now showed that TE is not accurate enough to differentiate among contiguous stages of fibrosis (especially between F0-1 and F2), but is sensitive enough to differentiate between the absence and mild fibrosis from significant fibrosis and cirrhosis, essential for the decision regarding treatment. At the same time, in the future we must find exactly if the histologi-

cal activity, the steatosis or the biological activity (ALT) have an important role in the assessment of LS by means of FibroScan, as shown in recent studies [16,21].

Several meta-analyses assessed LS measurements by TE as a predictor of significant fibrosis in patients with chronic hepatopathies [3,4,22,23]. In the Friedrich-Rust meta-analysis [3], the mean AUROC was 0.84, with a suggested optimal cut-off of 7.6 kPa for detecting significant fibrosis (F≥2) and the mean AUROC was 0.94, with an optimal cut-off of 13kPa for predicting cirrhosis. In a more recent meta-analysis published by Tsochatzis [23], which included 40 studies, the summary sensitivity and specificity for predicting significant fibrosis were 0.79 and 0.78, respectively. The mean optimal cut-off was 7.3±1.4 kPa (median 7.2 kPa). For predicting liver cirrhosis, the summary sensitivity was 0.83 and the summary specificity was 0.89, and the mean optimal cut-off was 15±4.1 kPa (median 14.5 kPa).

In the Tsochatzis meta-analysis [23] an analysis regarding the etiology of liver disease was also performed. Data regarding patients with chronic hepatitis C were extracted from 14 studies, and the summary sensitivity and specificity were 0.78 and 0.80 respectively for predicting significant fibrosis. Data regarding patients with chronic hepatitis B were extracted from 4 studies, and the summary sensitivity was 0.84 and the summary specificity was 0.78.

Regarding TE evaluation in patients with ***non-alcoholic fatty liver disease (NAFLD) and NASH***, a positive correlation was found between LS values and the histological stage of fibrosis [24]. LS measurements can be difficult in patients with NAFLD or NASH, since these conditions are often associated with obesity. A first step towards increasing the feasibility of TE in these patients was the introduction of the XL probe that increased the number of patients that could be evaluated by TE [25,26]. Wong et al evaluated TE (using standard M-probe) as a predictor of fibrosis and cirrhosis in NAFLD patients and the factors associated with discordance between TE and histology in 246 consecutive patients, who had successful LS measurements and satisfactory liver biopsy specimens [27]. The AUROCs of TE for severe fibrosis and cirrhosis were 0.93 and 0.95, respectively. At a cut-off value of 7.9 kPa, the sensitivity (Se), specificity (Sp), and positive (PPV) and negative predictive values (NPV) for F≥3 were 91%, 75%, 52%, and 97%, respectively. By multivariate analysis, LB specimen length less than 20 mm and F0-2 disease were associated with discordance between histological fibrosis and that predicted by TE.

A new technique, related to TE and performed with a FibroScan device is the Controlled Attenuation Parameter (CAP) and it enables steatosis quantification in fatty liver. CAP was significantly correlated to steatosis (r = 0.81) and the AUROCs for the detection of >10% and >33% steatosis were 0.91 and 0.95 respectively [28].

Regarding TE evaluation in patients with ***alcoholic liver disease (ALD),*** one must consider that in most of these patients, inflammation coexists with fibrosis and steatosis and it can influence the results of LS measurements. Higher cut-off values for cirrhosis were reported in patients with ALD, as compared to those with viral hepatitis: 19.5 kPa in the study by Nguyen-Khac et al [29] and 22.6 kPa in the Nahon study [30], but the patients included in those studies had high ALT levels that were not taken into consideration. Mueller et al [31] evaluated LS by TE in a cohort of patients admitted for alcohol detoxification, before and after normalization of serum transaminases. LS decreased in almost all patients (mean observation interval was 5.3 days). Of the serum transaminases, the decrease in LS correlated best with the decrease in glutamic oxaloacetic transaminase (GOT). No significant changes in LS were observed below GOT levels of 100 U/L. In the study cohort of 101 patients with histologically confirmed ASH, LS was measured only in patients with GOT<100 U/L at the time of LS assessment. In this group, the AUROC for cirrhosis detection by FS improved from 0.921 to 0.945 while specificity increased from 80% to 90%, at a sensitivity of 96%. A similar AUROC was obtained for F3 fibrosis stage, if LS measurements were restricted to patients with GOT <50 U/L [31].

Several studies proved that TE could be a valuable tool for assessing the ***severity of recurrent chronic hepatitis C, following liver transplantation,*** reducing the need for follow-up liver biopsies [32,33]. In a systematic review published in 2010, Cholongitas et al [34] showed that TE had a good discrimination power for significant fibrosis (median AUROC: 0.88, median Se: 0.86, median NPV: 0.90 and median PPV: 0.80). In a recent meta-analysis [35], the pooled data obtained from 5 studies that estimated at least F2 in transplant hepatitis C patients revealed 83% summary Se and Sp. Five studies assessed the predictive value for cirrhosis, and their pooled estimates were 98% for Se, 84% for Sp.

Transient Elastography was also studied for predicting ***liver cirrhosis complications***, especially ***portal hypertension***. Invasive evaluation of hepatic vein pressure gradient (HVPG) remains the "gold-standard" method for portal hypertension assessment. A HVPG value higher than 10 mmHg predicts the presence of clinically significant portal hypertension, while a value higher than 12mmHg is predictive for variceal bleeding [36]. The AUROC's for predicting clinically significant portal hypertension were 0.945 – 0.99, for cut-offs values ranging

between 13.6 and 21 kPa [37,38]. Also, the correlation of TE measurements with HVPG measurements was higher for patients with HVPG ≤ 12mmHg than in those with HVPG > 12mmHg [39]. Robic et al [40] evaluated 100 patients with chronic liver disease by TE and HVPG measurements performed in the same session, and followed them up for 2 years. HVPG and LS measurements showed similar performance for predicting portal hypertension: AUROCs 0.830 vs. 0.845. All patients with LS lower than the 21.1 kPa cut-off value remained free of portal hypertension complications during the 2 year follow-up, as compared to 47.5% of those with higher values. The performances of LS and HVPG were also similar in the cirrhotic subgroup of patients.

Several studies tried to predict by TE the presence of significant esophageal varices (at least grade 2). The proposed LS cut-off values ranged between 19.8 kPa and 47.5 kPa for predicting significant esophageal varices, with AUROC's between 0.72-0.78 [15,39,41,42]. More recently, Nguyen-Khac et al [43] demonstrated that there are different LS cut-off values for predicting significant esophageal varices, according to the etiology of cirrhosis. The cut-offs for predicting significant esophageal varices were: 47.2 kPa in alcoholic cirrhosis (84.6% Se, 63.6% Sp, AUROC=0.77) and 19.8 kPa in cirrhotic patients with viral etiology (88.9% Se, 55.1% Sp, AUROC=0.73). Other studies also provided cut-off values for predicting esophageal bleeding. The best cut-offs ranged between 50.7kPa – 62.7kPa, with AUROC's ranging between 0.73-0.75 [43,44].

A meta-analysis [45] including 18 studies with 3644 patients analyzed the usefulness of TE for predicting clinically significant portal hypertension and the presence of esophageal varices. Summary Se and Sp were 0.90 and 0.79 (AUROC=0.93) for significant portal hypertension; 0.87 and 0.53 (AUROC= .84) for esophageal varices; and 0.86 and 0.59 (AUROC=0.78) for significant esophageal varices respectively.

Hepatocellular carcinoma (HCC) is another feared complication of cirrhosis, being one of the most common causes of death in these patients. Several studies assessed the predictive value of LS by TE for the presence of HCC. In a study by Foucher et al [15], the cut-off value for the presence of HCC was 53.7 kPa. In a Japanese study [46], LS values in patients with HCC were significantly higher than in those without HCC. Multivariate analysis identified LS ≥12.5 kPa, age ≥60 years, and serum total bilirubin ≥1.0 mg/dL, as significantly correlated with development of HCC [46]. These data were similar to the ones from another Japanese study [47], that proved a significant increase in the risk of developing HCC that paralleled the increase of LS values, from 16.7 folds when LS was 10.1-15 kPa, to 20.9 folds when LS was 15.1-20 kPa, to 25.6 folds when LS was 20.1-25 kPa, and to 45.5 folds when LS was >25 kPa, as compared to patients with LS values<10 kPa.

II. ARFI quantification

Technique

Acoustic radiation force is a phenomenon associated with the propagation of acoustic waves in attenuating media [48,49].

The first step is to obtain a reference B-mode image of the region of interest by conventional ultrasound. Afterwards, the tissue is disturbed using a short acoustic pulse of hundreds of microseconds, which propagates through the tissue. As a result of energy transfer from the acoustic pulse to the tissue, a deformation process depending on the rigidity is produced. Soft tissues are elastic and will deform more than rigid tissue, whose elasticity is much lower. The deformation associated with high intensity ultrasonic pulse propagation is followed by a process of relaxation after which the tissue returns to its original configuration.

In the final phase, the region is scanned with a normal ultrasound beam and a new B-mode image is acquired. By comparing it with the reference image, displacements that occurred in different areas are calculated [48,49].

ARFI elastography is performed with a Siemens Acuson S2000TM ultrasound system (Siemens AG, Erlangen, Germany) with 4CI transducers. The same principle is used in a Phillips system. In the Siemens system, the operator can select the depth at which liver elasticity is evaluated, by placing a "measuring box" (10 mm long and 5 mm wide) in the desired place (fig 1). Scanning is performed by intercostal approach in the right liver lobe, to avoid cardiac motion (with the patient in supine position), with minimal scanning pressure applied by the operator, while the patient is asked to stop breathing for a moment, in order to minimize breathing motion. Usually, 10 valid measurements are performed and a median value is calculated (expressed in m/s). The measured value, as well as the measurements' depth, is displayed on the screen. If the measurement is not reliable, "X.XX" is displayed on the screen. The manufacturer initially did not recommend the use of technical parameters IQR and SR when the device was developed, but now they specify that especially the use of IQR parameter increase ARFI elastography accuracy for non-invasive liver fibrosis evaluation.

The best place for ARFI measurements seems to be at 1-2 cm under the liver capsule [50]. Goertz et al [51] demonstrated that ARFI assessments with the lowest rate

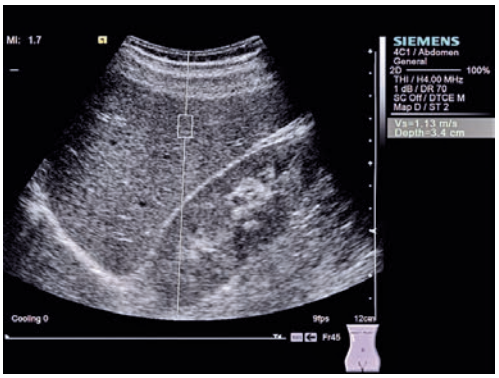

Fig 1. Ultrasound ARFI measurement in the liver acquired from the right intercostal space

of invalid measurements are obtained by an intercostal approach to segments VII/VIII of the liver, while Bota et al [52] demonstrated that similar ARFI values are obtained in segments VIII vs. V of the liver.

Clinical applications

Similar with TE, ARFI was first used and validated in patients with ***chronic hepatitis C***, and afterwards in other etiologies of chronic liver diseases. The first data were published by Friedrich-Rust et al [53]. In this study, the AUROCs of ARFI, TE, FibroTest and APRI for predicting F ≥ 2 were: 0.86, 0.87, 0.86, and 0.81 respectively; for predicting F ≥ 3: 0.93, 0.90, 0.93 and 0.80 respectively, while for predicting F=4 they were: 0.95, 0.91, 0.84 and 0.73 respectively. The best LS cut-off values assessed by ARFI for predicting F ≥2, F≥3 and F=4 were: 1.35 m/s, 1.55 m/s and 1.75 m/s respectively.

Other published studies showed cut-offs for LS assessed by ARFI ranging from 1.21 to 1.34 m/s for predicting significant fibrosis (F≥2), with AUROC's ranging between 0.85-0.89 [54-56], while for predicting cirrhosis the ARFI cut-offs ranged between 1.8-2 m/s, with AUROC's between 0.89-0.93 [54-56].

In a retrospective international multicenter study [57] which included 914 patients with chronic hepatitis C (10 centers, 5 countries from Europe and Asia), all patients were evaluated by means of LB and ARFI, and in a subgroup of patients also by means of TE. A highly significant correlation (r=0.654) was found between ARFI measurements and fibrosis (p<0.0001), being significantly higher in European as compared with Asian patients: r=0.756, p<0.0001 vs. r=0.544, p<0.0001 (p<0.0001). The predictive values of ARFI for various stages of fibrosis were: F≥1 – cut-off >1.19 m/s (AUROC=0.779); F≥2 – cut-off >1.33 m/s (AUROC=0.792); F≥3 – cut-off >1.43 m/s (AUROC=0.829); F=4 – cut-off >1.55 m/s (AUROC=0.842). The cut-offs for predicting significant fibrosis and cirrhosis were different in European vs. Asian subjects: 1.21 m/s (AUROC=0.857) and 1.74 m/s (AUROC=0.892) in European patients, and 1.32 m/s (AUROC=0.736) and 1.55 m/s (AUROC=0.736) in Asian patients. Also, in this study a large overlap of ARFI measurements was found for F0 to F2 and only severe fibrosis and cirrhosis could be excluded with great certainty, similarly to the findings already reported with TE.

Regarding the use of ARFI elastography for the evaluation of liver fibrosis in patients with ***chronic hepatitis B***, Sporea et al [58] evaluated 160 patients (53 with chronic hepatitis B and 107 with chronic hepatitis C) by means of LB, ARFI and TE measurements. The correlation of LS measurements assessed by means of ARFI elastography with histological liver fibrosis was similar in patients with chronic hepatitis C vs. those with chronic hepatitis B: r=0.490, p<0.0001 vs. r=0.356, p=0.01 (p=0.36). The mean LS values assessed by ARFI elastography were similar for the same stage of histological fibrosis in patients with chronic hepatitis B and C.

In a German multicenter study performed by Friedrich Rust et al [59], in which ARFI was evaluated as a predictor of fibrosis severity in patients with chronic hepatitis B, 133 subjects were included, 79% of them evaluated also by means of TE. In this study, ARFI and TE were significantly correlated to the histological fibrosis stage. In this cohort of patients, the AUROCs for ARFI were 0.69 for significant fibrosis, 0.83 for severe fibrosis and 0.96 for liver cirrhosis. No differences were found between ARFI and TE for the diagnosis of F≥2, F≥3 and F=4.

In a retrospective international multicenter study [60] comprising 1095 patients (181 with chronic hepatitis B and 914 with chronic hepatitis C) from Europe and Asia, evaluated by means of LB and ARFI elastography, the correlation of LS assessed by ARFI elastography with histological fibrosis was significantly better in chronic hepatitis C patients as compared with those with chronic hepatitis B: r=0.653, p<0.0001 vs. r=0.511, p<0.0001 (p=0.007). The mean LS values as determined by ARFI elastography, depending on the stage of fibrosis in patients with chronic hepatitis B and C, were also similar.

A recently published meta-analysis [61] included 13 studies in which 1163 patients with chronic liver diseases were evaluated by means of LB (considered the "gold-standard" method), ARFI elastography and TE. For detection of significant fibrosis (F≥2) the summary Se and Sp were 0.74 and 0.83 for ARFI elastography, while for TE the summary Se and Sp were 0.78 and 0.84. For the diagnosis of cirrhosis the summary Se and Sp were 0.87 and 0.87 for ARFI, and respectively 0.89 and 0.87 for TE. The diagnostic odds ratio of ARFI and TE did not

differ significantly for the detection of significant fibrosis and cirrhosis. The median optimal cut-off value of LS assessed by ARFI for the detection of significant fibrosis and cirrhosis were 1.31 m/s and 1.8 m/s, respectively.

The value of ARFI elastography for predicting fibrosis severity in patients with ***NAFLD and NASH*** was also evaluated. The cut-offs for LS assessed by ARFI ranged between 1.47-1.77 m/s for predicting severe fibrosis (F≥3), with AUROC's between 0.71-0.97 [62, 63], while for predicting cirrhosis, the ARFI cut-offs ranged between 1.77-2 m/s, with AUROC's between 0.74-0.97 [62,63]. The predictive value of ARFI and TE performed with the M-probe were similar for detecting severe fibrosis and liver cirrhosis [35].

Regarding the evaluation of ***post-transplant patients*** by means of ARFI elastography, Crespo et al [64] evaluated 62 liver transplanted patients by means of LB, ARFI, TE and serological tests. The correlation between ARFI and TE measurements was very good (r=0.886). The AUROCs for predicting significant fibrosis were 0.921, 0.898, 0.803 and 0.801 for ARFI, TE, ELF and APRI score, respectively.

ARFI elastography was also studied for predicting ***complications of liver cirrhosis***, especially ***portal hypertension***. Salzl et al [65] presented the first data regarding the correlation of ARFI measurements with HVPG in 48 patients, and a very good correlation was observed (r= 0.709). The authors obtained a good performance of ARFI elastography for predicting clinically significant portal hypertension (AUROC = 0.874). Borghi et al [66] did not find a correlation between LS measurements assessed by ARFI and HVPG measurements, but they found a significant correlation between spleen stiffness (SS) assessed by ARFI and HVPG (r=0.749).

In the study published by Şirli et al [67], the mean LS values assessed by ARFI were similar in patients with and without significant esophageal varices. Vermehren et al [68] evaluated 166 cirrhotic patients, and an AUROC of 0.58 for predicting significant esophageal varices was obtained. Rifai et al [69] evaluated 125 subjects (healthy control subjects and patients with chronic hepatopathies, with or without portal hypertension). In this study, a significantly better performance of LS as compared with SS for predicting significant portal hypertension was observed (AUROC 0.90 vs. 0.68), but the LS cut-off value proposed for predicting significant portal hypertension (1.67 m/s) is lower than the ARFI cut-off values proposed by most published studies for diagnosing liver cirrhosis [53-57].

A solution to increase the value of ARFI elastography seems to be the combination of different parameters, such as LS, SS and the presence of ascites [70].

Regarding the prediction of ***HCC occurrence***, Şirli et al [67] found similar mean LS values assessed by ARFI in patients with and without HCC, while Vermehren et al [68] obtained an AUROC curve of 0.54 for predicting the occurrence of HCC.

As compared with TE, ARFI elastography can be used also in patients with ascites and it was studied for predicting the ***decompensation of liver cirrhosis***. Şirli et al [67] observed significantly higher ARFI values in patients with decompensated liver cirrhosis as compared with those with compensated cirrhosis. Bota et al [71] obtained an AUROC of 0.65 for a cut-off value of 3.11 m/s, for predicting the presence of at least B class Child-Pugh cirrhosis.

III. Real Time Shear Wave Elastography (SWE)

Technique

To obtain a quantitative elasticity map of the medium, we need to image the propagation of the shear-wave and to measure its velocity. The shear waves typically propagate at a few m/s, thus a frame rate of several kilohertz is needed. This is not possible using conventional ultrasound scanners (they typically reach a 50-Hz frame rate). Thus the use of an ultrafast ultrasonic scanner is required, able to remotely generate the mechanical shear wave, by focusing ultrasound at a given location, and image the medium during the wave propagation at a very high-frame rate (up to 6000 images/s). The ultrafast frame rate is achieved by reducing the emitting mode to a single, plane-wave insonation. This technique allows the acquisition of echographic images at a pulse repetition that can reach 6000 Hz. The final data may be displayed in units of shear wave velocity (m/s) or converted into units of Young's modulus (kPa) [72].

The technique is available on the Aixplorer® system (SuperSonic Imagine, France). The patient is placed in

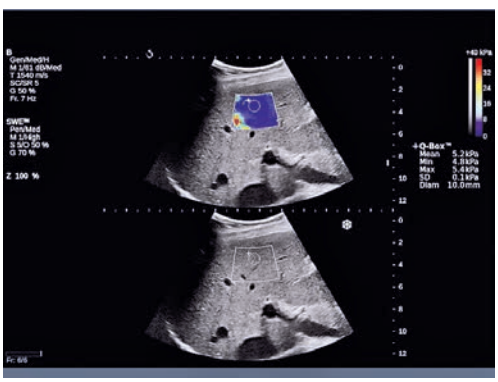

Fig 2. SWE (Aixplorer) ultrasound image of the liver in a normal subject, acquired from the right intercostal space.

supine position with the right arm in maximum abduction. The convex probe is placed between the ribs, using the best acoustic window available for liver evaluation. It is recommended to perform the acquisition on the right liver lobe and slow or no movement of the probe is preferable in order to avoid motion artifacts and to allow map stabilization. The SWE™ box has to be placed in vessel free parenchyma, in a uniform zone, not too close to the liver capsule (fig 2). The patient has to hold breath in the expiration phase to acquire a stable image. The quantification box is next placed in a homogeneous area and the elasticity value is displayed on the image. This method can be used in patients with ascites similar to ARFI elastography.

Clinical applications

The first clinical study was published by Bavu et al [73] who evaluated 133 patients with chronic hepatitis C by means of SWE, TE and, in a subgroup of patients, also by means of LB. The AUROCs for elasticity values assessed by SWE were: 0.948 for significant fibrosis, 0.962 for severe fibrosis and 0.968 for liver cirrhosis. In this study, the AUROCs for SWE were better than those from TE performed in the same session for F≥2, F≥3 and F4.

Ferraioli et al [74] compared SWE with TE and LB. The cut-off value found for F≥2 was 7.4 kPa (AUROC=0.91), for F≥3 it was 8.7 kPa (AUROC=0.99) and for F=4 it was 9.2 kPa (AUROC=0.97). In cases in which SWE was compared to TE, the two methods showed similar diagnostic performance.

Because only a few studies were published, more information is needed for the introduction of this method in clinical practice.

One study tried to compare the feasibility of three shear waves elastographic methods [75]. In a cohort of 332 patients, with or without hepatopathies, LS was evaluated by TE, ARFI and SWE. Reliable measurements were obtained in a significantly higher percentage by means of ARFI as compared with TE and SWE: 92.1% vs.72.2% ($p<0.0001$) and 92.1% vs. 71.3% ($p<0.0001$). Higher BMI and older age were significantly associated with impossibility to obtain reliable measurements of LS for TE and SWE. In subjects in whom reliable LS measurements were obtained by all three elastographic methods, the accuracy was similar for ARFI and SWE for diagnosing significant fibrosis and cirrhosis, considering TE as reference method.

IV. Strain Elastography – Real-Time Elastography (RT-E)

Technique

When an elastic medium is compressed with a constant, axial oriented pressure, all points of the environment support a longitudinal deformation, whose main component is oriented on the axis of compression. If one or more tissue constituent elements have a different stiffness than the others, their deformation will be different. Longitudinal deformation is estimated by analyzing the ultrasonic signals obtained with conventional equipment in the following sequence [76]: the region of interest is scanned and the set of appropriate radio-frequency echoes is digitized and stored; a tissue compression force is applied to produce small linear elastic deformation into the tissue and the region of interest is scanned once again and a new set of echo signals is acquired.

Pairs of signals who correspond to the same directions of scanning are subdivided into small time windows and then compared using cross-correlation techniques. The windows are translated in small overlapping steps along the temporal axis of the echo line, and the calculation is repeated for all depths. For each direction and for each focal point in the direction considered, the differences between ultrasound wave propagation times are determined in two situations. Since the compressive stress amplitude is small, deformation and thus differences in propagation times will also be reduced. This technique is called "quasi-static" elastography [7]. Initially, hand compression was used for tissue deformation, but, more recently, heart beatings are used to stress the tissue.

Real-Time Elastography (RT-E) using a clinical scanner was performed for the first time with Hitachi systems (EUB-8500 and EUB-900). It uses a conventional ultrasound probe to compare and analyze echo signals before and under slight compression. To evaluate LS by means of RT-E, the patient is positioned in supine position and the transducer is placed between the ribs while the examiner applies stress by moving the transducer [77]. The examination is usually performed in the right liver lobe (fig 3). The Hitachi SonoElastography (HI-RTE) module uses an extended combined autocorrelation method to produce a real-time elasticity image, by using a freehand approach to compress the tissues with the ultrasound transducer. The relative tissue elasticity is calculated and displayed as a color overlay on the conventional B-mode image. Stiffer tissue structures are displayed in blue, while the more easily deformed tissues (softer tissue structures) are displayed in red. Recently, a new system from Hitachi has been made available (HI VISION Preirus, Hitachi Medical Systems Europe Holding AG, Zug, Switzerland), in which a linear probe automatically captures the internal compression produced by the heartbeat on the liver parenchyma.

Clinical applications

The first data regarding chronic hepatitis evaluated by HI-RTE (Hitachi EUB-8500 and EUB-900) were

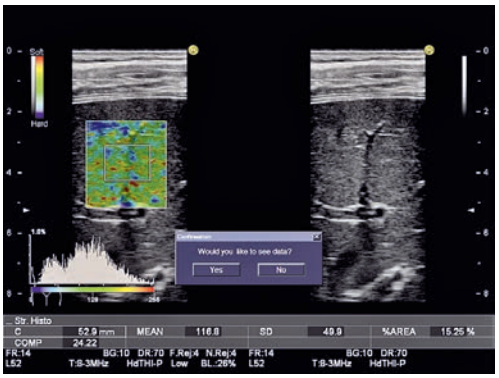

Fig 3. Histogram evaluation in RT-E

published by Friedrich-Rust el al [78]. The investigators attempted to find a new elasticity score using a specially developed Matlab computer program. By using stepwise multivariate logistic regression analysis, the authors developed the following formula: Elasticity score=177+50× Log_{10}Median[Freq(pixel≥0.75)]–13,000×Min[Min(pixel with values >0)]. This elasticity score ranged from 65 to 122. The accuracy was 0.75 for F≥2, 0.73 for F≥3 and 0.69 for F=4.

Tatsumi et al [79] performed HI-RTE in 119 patients with chronic liver disease and compared the results with LB, TE and serum markers. The authors elaborated the Japanese Elasticity Score: numerical values were determined from 0 – 255 according to color mapping from blue (0) to red (255), followed by the calculation of means±SD in the "region of interest" (ROI), the percentage of blue area in the ROI, the complexity (length squared divided by blue area), skewness, as well as image features using a co-occurrence matrix: inverse difference moment, angular second moment (ASM), and entropy. In this study HI-RTE showed a negative correlation with fibrotic stages and TE findings, suggesting that real-time tissue elastography is a better test than TE.

Fujimoto et al [80] evaluated the effectiveness of RT-E for liver fibrosis assessment in a cohort of 310 patients with chronic hepatitis C. Nine image features were extracted from each RT-E image and multiple regression analysis was performed to obtain an equation for the Liver Fibrosis Index (LF Index), which had 78.4% accuracy to discriminate between patients with or without severe fibrosis and 80.3% accuracy to discriminate between those with or without liver cirrhosis.

Another improvement in this technique was the development of the new HI VISION Preirus (Hitachi Medical Systems Europe Holding AG) system with embedded elastography module. The linear probe (3.5-7MHz) is applied in an intercostal space without compression. The strain graph displayed is used as a quality control of the procedure. The device automatically captures the internal compression transmitted to the liver parenchyma by the heartbeat. A 3-4 seconds loop must be recorded, from which several frames representing the negative peaks in the strain graphs are extracted. On each image the histogram and the parameter values are displayed. This new system was used by Colombo et al [81] which evaluated 45 patients with chronic liver diseases and 27 normal subjects by means of TE, ARFI and RT-E. The AUROCs for predicting significant fibrosis (F≥2) for TE, RT-E and ARFI were 0.897, 0.751 and respectively 0.815 (TE was significantly better than RT-E and no significant difference between TE and ARFI, nor between ARFI and RT-E). The AUROCs for predicting liver cirrhosis (F=4) for TE, RT-E and ARFI were 0.922, 0.852 and respectively 0.934 (no significant difference between the three curves were observed). Another two Japanese studies [82, 83] showed good results for the evaluation of liver fibrosis:Yada et al [83] evaluated 245 patients with chronic hepatitis B and C. Nine parameters from the histogram and Liver Fibrosis Index (LFI) were compared to the LB. In this study, the AUROC for LFI was 0.800 to discriminate between F0-1 vs. F2-4 and 0.846 to discriminate between F0-3 vs. F4. In another study, Fujimoto et al [82] compared LFI to LB in a cohort of 310 subjects. In 15% of cases no valid measurements were obtained. LFI highly correlated with fibrosis stages ($r=0.68$ with $p<0.001$) and the AUROC of LFI for differentiating F0-1 vs. F2-4 was 0.82. One very important conclusion of this study was that LFI seems not to be correlated with inflammation (unlike other elastographic methods).

In **conclusion** of this update on liver elastography using ultrasound waves, we can say that the elastographic methods showed good results for the evaluation of liver stiffness as a predictor of fibrosis severity (especially for moderate to severe fibrosis). These methods are increasingly used in daily practice (especially Transient Elastography) while the other elastographic methods try to prove their value in clinical studies. In the near future, these elastographic methods will decrease the need for liver biopsy in many patients with chronic liver diseases.

Conflict of interest: none

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