Estimation of liver stiffness using ultrasound waves

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Content

Introduction

In the evolution of chronic viral and non-viral hepatitis, liver fibrosis is a very important factor associated with prognosis. Hence, a precise evaluation of the severity of fibrosis is necessary in those patients, in order to perform a correct staging and, eventually, to take a decision regarding the treatment.

Currently, liver biopsy seems to be the optimal method to evaluate changes in fibrosis over time (1). Nevertheless, liver biopsy (LB) has its shortcomings: the intra- and interobserver variability (2, 3), the sampling variability (as proven in a study by Ratziu et al) (4) and, last, but not least, the fact that LB is an invasive method, with morbidity and mortality greater than zero.

Considering all these facts, non invasive methods for the evaluation of liver fibrosis were developed in the last few years, in order to reduce the number of LB. A real polemic developed in the last years, regarding the best method to evaluate these patients, opposing the liver biopsy (LB), still considered being the “gold standard” for hepatological evaluation (5), to the non-invasive methods of assessment, recently developed. The difficulty in the evaluation of non-invasive markers, is that liver biopsy is used as reference method. Taking into account the limitations of liver biopsy, a perfect non-invasive method can not be distinguished from an unacceptable fibrosis marker. Therefore a new reference marker is needed. Studies using the endpoint liver related mortality are awaited to identify the best non-invasive methods.

After 2000, the non-invasive tests predictors of fibrosis were evaluated mainly in C chronic hepatitis, but many articles regarding the usefulness of these methods in other chronic hepatopathies were published in the last years.

The underlying assumption using non-invasive methods is that liver disease progression is associated with changes in tissue strain, that can be measured by elastography. In general
terms, strain is a measure of tissue deformation due to an imposed force (stress) (7). It represents the fractional change from the original or unstressed dimension (Lagrangian strain), includes both lengthening, or expansion (positive strains) and shortening, or compression (negative strains)(8).

The non-invasive methods for assessing the severity of fibrosis are: serum markers (the best known is FibroTest-ActiTest – a biochemical test which uses 6 serum biomarkers, correlated to the age and gender of the patient in a mathematical formula) (6, 9-11), and MRI elastography (13, 14). Using ultrasound technology there are several methods that can be applied to study strain and elasticity of the liver. Ophir et al developed ultrasonic methods for quantitative imaging of strain and elastic modulus distributions in soft tissues (15, 16). This method is based on external tissue compression with subsequent computation of the strain profile along the transducer axis. The temporal derivative of strain, i.e., the strain rate, is a measure of the rate of deformation. Strain Rate Imaging is a Doppler-based method that can be used to measure strain of moving tissue (17-19), but it can also be applied for the liver by inducing probe pressure.

Recently, in vivo quantitative mapping of liver viscoelasticity was also be performed using the concept of supersonic shear wave imaging (20). This technique is based on the combination of a radiation force induced in tissues by focused ultrasonic beams and a very high frame rate (up to 5000 f/sec) ultrasound images capable of catching, in real time, the transient propagation of resulting shear waves (21, 22). The local shear wave velocity is recovered using a dedicated time-of-flight estimation technique and enables the 2-D quantitative mapping of shear elasticity. This imaging modality can be performed using a conventional ultrasound probe, during a standard intercostal ultrasonographic examination. Three supersonic shear imaging (SSI) sequences are applied successively in the left, middle and right parts of the 2-D ultrasonographic image. Resulting shear elasticity images in the three regions are concatenated to provide the final image covering the entire region-of-interest. The ability of the SSI technique to provide a quantitative and local estimation of liver shear modulus with a millimetric resolution was proven in a pilot study in 15 healthy volunteers (20). Liver moduli extracted from in vivo data, from healthy volunteers, were consistent with those reported in the literature (Young's modulus ranging from 4 to 7.5 kPa). Moreover, liver stiffness estimation using the SSI mode was fast (less than one second), repeatable (5.7% standard deviation) and reproducible (6.7% standard deviation).

For clinical purposes, the following ultrasound methods has been most frequently applied to estimate liver fibrosis: Transient Elastography (TE) (FibroScan) (12, 23, 24), Real-Time
**Tissue Elastography** (HiRT-E, Hitachi) (25-29), **Acoustic Radiation Force Impulse (ARFI)** (Siemens) (31-34)

**Transient elastography (TE)** is an ultrasound-based method, based on the principle of Hooke’s law, which characterizes a material’s strain response to external stress (23). By using an ultrasound transducer probe mounted on the axis of a vibrator, the transmission of low-frequency vibrations from the right intercostal space creates an elastic shear wave that propagates into the liver. A pulse-echo ultrasound acquisition is then used to detect the velocity of wave propagation. This velocity is proportional to the tissue stiffness, with faster wave progression occurring through stiffer material. Measurement of liver stiffness (LS) is then performed and measured in kilopascals (kPa) (35) (values between 2.5 and 75 kPa). Transient elastography is performed with FibroScan (Echosens, Paris, France).

**Figure 1** The FibroScan device.
Figure 2  The FibroScan probe.

Figure 3  TE measurement by means of FibroScan, adapted from Sandrin L et al (47).
Using this method, measurements were performed in the right lobe of the liver through the intercostal spaces, while the patients were lying in dorsal decubitus position with the right arm in maximal abduction. The tip of the transducer was covered with coupling gel and placed on the skin, between the ribs, aiming at the right lobe of the liver. The operator, assisted by ultrasound A-mode images provided by the system, located a portion of the liver that was at least 6 cm thick, free of large vascular structures. Once the area of measurement had been located, the operator pressed the probe button to begin an acquisition. Acquisitions that did not have a correct vibration shape or a correct follow-up of the vibration propagation were automatically rejected by the software.

The TE assessment of LS was validated as method of evaluation in chronic hepatitis C. Also, there are some articles, recently published, that proved the value of this method in other chronic hepatopathies (like HBV infection, haemochromatosis, primary biliary cirrhosis, HIV/HCV coinfection or non-alcoholic steato-hepatitis) (36-42).

Some studies and meta-analysis (23, 24) suggested that the FibroScan evaluation of LS is a reproducible method, with low inter- and intraobserver variability (43-47), with a rate of successful measurements of 94-97% (43), thus making it useful for daily practice. However, while showing excellent results for the diagnosis of liver cirrhosis, the differentiation of mild from significant fibrosis is only moderate (23, 24).

Based on the studies presented above we would suggest the use of FibroScan measurement of LS in two situations:

1. When liver cirrhosis is suspected, based on anamnesis, clinical and biological data, but not obvious on B-mode ultrasound (but the evaluation is not possible when ascites is present).
The LS measurement by means of FibroScan is a reliable method for the diagnosis of cirrhosis, with 87% sensitivity (95%CI: 84-90%), 91% specificity (95%CI: 89-92%), with 11.7 positive likelihood ratio (95%CI: 7.9-17.1) and 0.14 negative likelihood ratio (95%CI: 0.10-0.20), as shown in a meta-analysis performed by Talwalkar et al. (23). The advantage of FibroScan evaluation of liver fibrosis, on other non-invasive methods, is that transient elastography can also assess the severity of cirrhosis (values up to 75 kPa), as shown in some studies which proposed cut-off values of LS that predict the presence of cirrhosis complications (esophageal varices, variceal bleeding, vascular decompensation or hepatocellular carcinoma) (48-53).

2. The second clinical application of LS measurement by means of TE is the evaluation of patients with chronic C viral hepatitis. In viremic patients, if the LS is greater than 6.8–7.6 kPa (according to the results of several studies and meta-analysis) (23, 24, 35, 54-56), there is a great probability of finding significant fibrosis on liver biopsy (F2-F4), thus the patient needing antiviral therapy. Probably, in these cases, LB is not needed for treatment decision.

In a multicentre French study coordinated by Beaugrand (56), performed on 494 HCV patients who were evaluated by means of percutaneous LB (with a significant fragment) and valid FibroScan examination, a significant correlation was found (p<0.001) between the severity of fibrosis and the values of LS measured by means of TE (r=0.57). This study tried to establish cut-off values for the LS that could differentiate between various stages of fibrosis. Thus, the cut-off value of 7.5 kPa differentiates F0-1 from F2-4 with 67% sensitivity, 87% specificity, 86% PPV and 68% NPV, with a diagnostic accuracy of 76%. Other studies (35, 54-56) established cut-off values that differentiate F0-1 from F2-4 ranging from 6.8-7.3 kPa. As a practical approach, viremic patients with LS lower than 7 kPa should undergo LB in order to discover the ones with significant fibrosis underestimated by FibroScan and who, otherwise, would not receive antiviral therapy. This strategy is already used in France, a country in which non-invasive evaluation of chronic C viral hepatitis is used more and more frequently.

TE is not accurate enough to differentiate among contiguous stages of fibrosis (especially 0, 1 and 2), but is sensitive enough to differentiate between the absence and mild fibrosis from significant fibrosis, essential for the decision regarding treatment. In the same time, in the future we must find exactly if histological activity, steatosis or biological activity (ALT) have an important role in the assessment of LS by means of FibroScan, as shown some recent studies (57, 58).
In a study performed in Romania (57) on 324 consecutive patients chronically infected with hepatitis C virus, evaluated both by FibroScan and LB in the same session, the LS values were strongly correlated with fibrosis ($r=0.759$, $p<0.0005$), but also with steatosis ($r=0.255$, $p<0.005$), necroinflammatory activity ($r=0.378$, $p<0.0005$) and hepatic iron deposition ($r=0.143$, $p=0.03$). The univariant regression analysis demonstrated that fibrosis ($R^2=0.610$, $p<0.0005$), activity ($R^2=0.145$, $p<0.0005$) and steatosis ($R^2=0.037$, $p<0.002$) were correlated with LS. In multiple regression analysis, all three variable independently influenced LS: fibrosis ($p<0.0005$), activity ($p=0.039$) and steatosis ($p=0.025$). The conclusions of this study were that fibrosis is the main predictor of LS, but also that it is influenced by the disease activity and steatosis.

In a study performed by Coco and co-workers (58), the value of LS was evaluated considering the level of aminotransferases, proving that another factor than fibrosis, independently associated with LS was ALT for patients with chronic hepatitis. The LS dynamics profiles paralleled those of ALT, increasing 1.3 to 3 fold during ALT flares. This study showed that the LS remained unchanged in patients with stable biochemical activity.

Considering all these data, we could use the FibroScan evaluation of LS in patients with chronic HCV hepatitis for decisions regarding therapy. All these studies showed that, by using cut-off values of 6.8–7.6 kPa, we could identify accurately enough the patients who need to be treated ($F \geq 2$ METAVIR) versus those who should not be treated ($F < 2$ METAVIR), without performing a LB. Combining FibroScan with serum fibrosis markers can further improve the diagnostic accuracy of non-invasive liver fibrosis measurement (35) and different algorithms have been suggested.

3. The FibroScan can be used for individual follow-up of patients to detect a progression of liver disease and possibly then initiate therapy.

Regarding the value of LS evaluated by means of TE in evaluating chronic hepatopathies of other etiologies, several studies were performed in the last time, in order to identify significant fibrosis in patients with HBV chronic hepatitis (39, 58), in HIV-HCV co-infection (37, 40), in chronic cholestatic hepatopathies: primary biliary cirrhosis (PBC) and primary sclerosing colangitis (PSC) (36) and in NASH (41, 42). In these studies, the area under the ROC curve varied between 0.72 and 0.93, and the cut-off values for $F \geq 2$ ranged between 4 and 8.7 kPa (Table 1).
In order to assess the value of TE for predicting fibrosis, a first meta-analysis was performed by Talwalkar and co-workers (23), based on nine in extenso published studies (7 of them assessing the value of TE for predicting significant fibrosis). This meta-analysis confirmed the value of LS for predicting significant fibrosis, with overall 70% sensitivity (95% CI: 67-73%), 84% specificity (95% CI: 80-88%) and AUROC=0.87.

A more recent meta-analysis performed by Friedrich-Rust (24) on 50 studies (15 extended articles and 35 abstracts) also assessed the value of TE for the diagnosis of significant fibrosis. Thus, the overall AUROC was 0.84 (95% CI: 0.82-0.86).

Both meta-analyses emphasized the heterogeneity of results (variations of the AUROC), if the etiology of the liver disease (p<0.001) is taken into consideration.

In his meta-analysis, Talwalkar (23) has shown excellent performance of TE for the diagnosis of liver cirrhosis (LC) with 87% sensitivity (95% CI: 84-90%), 91% specificity (95% CI: 89-92%) and 0.14 negative likelihood ratio (95% CI: 0.1-0.2). Again, a certain heterogeneity due to different etiologies has been mentioned, thus the LS cut-off values varied from 11 kPa in

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**Tabelle 1** Performance of LS for evaluating significant fibrosis in patients with chronic hepatopathies other than HCV (PPV = positive predictive value, NPV = negative predictive value).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Etiology</th>
<th>No. of patients</th>
<th>Proposed cut-off (kPa)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>NPV (%)</th>
<th>PPV (%)</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraquelli et al. (45)</td>
<td>Diverse</td>
<td>100</td>
<td>7.9</td>
<td>72</td>
<td>84</td>
<td>70</td>
<td>82</td>
<td>0.86</td>
</tr>
<tr>
<td>Coco et al. (58)</td>
<td>HCV-HBV</td>
<td>141</td>
<td>8.3</td>
<td>85.2</td>
<td>90.7</td>
<td>78.8</td>
<td>93.5</td>
<td>0.93</td>
</tr>
<tr>
<td>Marcellin et al. (39)</td>
<td>HBV</td>
<td>87</td>
<td>7.2</td>
<td>70</td>
<td>83</td>
<td>73</td>
<td>80</td>
<td>0.81</td>
</tr>
<tr>
<td>De Ledinghen et al. (37)</td>
<td>HCV-HIV</td>
<td>44</td>
<td>4.5</td>
<td>93.2</td>
<td>17.9</td>
<td>61</td>
<td>65</td>
<td>0.72</td>
</tr>
<tr>
<td>Vergara et al. (40)</td>
<td>HCV-HIV</td>
<td>105</td>
<td>7.2</td>
<td>88</td>
<td>66</td>
<td>75</td>
<td>88</td>
<td>0.83</td>
</tr>
<tr>
<td>Corpechot et al. (36)</td>
<td>PBC and NAFLD</td>
<td>57</td>
<td>7.3</td>
<td>84</td>
<td>87</td>
<td>79</td>
<td>91</td>
<td>0.92</td>
</tr>
<tr>
<td>Yoneda et al. (42)</td>
<td></td>
<td>33</td>
<td>6.6</td>
<td>82.7</td>
<td>81.3</td>
<td></td>
<td></td>
<td>0.87</td>
</tr>
</tbody>
</table>
patients with chronic HBV hepatitis (27) up to 17.3 kPa in chronic cholestatic hepatopathies (36) (Table 2).

### Tabelle 2
Performance of TE for the diagnosis of LC considering the etiology (Se – sensitivity; Sp – specificity; NPV – negative predictive value; PPV – positive predictive value).

<table>
<thead>
<tr>
<th>Author</th>
<th>Etiology</th>
<th>No of patients</th>
<th>Cut-off values (kPa)</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>NPV (%)</th>
<th>PPV (%)</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraquelli et al. (45)</td>
<td>Diverse</td>
<td>24</td>
<td>11.9</td>
<td>91</td>
<td>89</td>
<td>98</td>
<td>98</td>
<td>0.90</td>
</tr>
<tr>
<td>Coco et al. (58)</td>
<td>HCV-HBV</td>
<td>46</td>
<td>14</td>
<td>78</td>
<td>98</td>
<td>82</td>
<td>82</td>
<td>0.96</td>
</tr>
<tr>
<td>Marcellin et al. (39)</td>
<td>HBV</td>
<td>14</td>
<td>11.0</td>
<td>93</td>
<td>87</td>
<td>95</td>
<td>95</td>
<td>0.93</td>
</tr>
<tr>
<td>De Ledinghen et al. (37)</td>
<td>HCV-HIV</td>
<td>17</td>
<td>11.8</td>
<td>100</td>
<td>92.7</td>
<td>82</td>
<td>94</td>
<td>0.97</td>
</tr>
<tr>
<td>Vergara et al. (40)</td>
<td>HCV-HIV</td>
<td>65</td>
<td>14.6</td>
<td>93</td>
<td>88</td>
<td>94</td>
<td>94</td>
<td>0.95</td>
</tr>
<tr>
<td>Corpechot et al. [36]</td>
<td>PBC - CSP</td>
<td>15</td>
<td>17.3</td>
<td>93</td>
<td>95</td>
<td>99</td>
<td>96</td>
<td>0.96</td>
</tr>
<tr>
<td>Yoneda et al. [42]</td>
<td>NAFLD</td>
<td>5</td>
<td>17.0</td>
<td>100</td>
<td>98</td>
<td>98</td>
<td>96</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Another meta-analysis (31) included 38 studies reporting data regarding the AUROC in cases with LC. The mean AUROC for the diagnosis of LC was 0.94 (95%CI: 0.93-0.95). It is worth mentioning that no differences were found regarding the AUROC depending on the etiology of cirrhosis.

So, which are the disadvantages of TE assessment of fibrosis by means of FibroScan: impossibility to discriminate between the various contiguous degrees of fibrosis, false overestimated results during ALT flares, high cost of the machine (approximately 80,000 Euros), and measurement failure in patients with ascites. In this moment, worldwide there are more than 250 centers in which TE is performed.
**Real-Time Elastography**

Despite the fact that fibrosis is considered to be homogenous into the liver, probably it is better to choose the area of examination using B-mode ultrasound. TE makes a “semi-blind” evaluation of LS, having the capacity to avoid the presence of large vessels. Recent development of performant, dedicated ultrasound machines, made possible the use of these tools to evaluate, in “real-time”, the elasticity of the liver tissue.

Elastography is an ultrasound based imaging method, which can display local differences in tissue stiffness by recording tissue strain in response to stress, applied in a repetitive manner (59, 60). Real-time elastography (RT-E) is a method that evaluates tissue elasticity, and is technically different from TE (61, 62).

**Real-Time Elastography** performed with the Hitachi system (EUB-8500 and EUB-900) was the first one that appeared on the market (25) and uses a conventional ultrasound probe, echo signals before and under slight compression being compared and analyzed (61). For performing free-hand real-time elastography, the investigator must apply stress by moving the transducer (63).

The **Hitachi SonoElastography (Hi RT-E)** module uses an Extended Combined Autocorrelation Method to produce a “real-time” elasticity image, using a freehand approach to compress the tissues with the ultrasound transducer. The relative elasticity of the tissues is calculated and displayed as a color overlay on the conventional B-mode image, the stiffer tissue structures being displayed as blue, whilst the more easily deformed tissues are displayed in red (from Hitachi Medical Systems).

HiRT-E uses the combined autocorrelation method to rapidly calculate the relative stiffness of the tissue based on tissue distortion, and displays this information as “real-time” color images (64, 65).
This method has been used in clinical practice for the assessment of focal lesions in the breast, thyroid, prostate and pancreas (64, 65) and, more recently, for the evaluation of hepatic fibrosis (62, 66-68).

The first report (62) regarding chronic hepatitis evaluated by means of real-time elastography (HiRT-E) (Hitachi EUB-8500 and EUB-900) included 79 patients with chronic HCV or HBV hepatitis (all of them with LB), 20 patients with proven cirrhosis and a control group of 20 healthy volunteers. In those subjects, the amount of displacement of the reflected ultrasound echoes before and under compression were measured (stress field). In a second time, a strain field is reconstructed from the measured displacements (strain image). The calculation of tissue elasticity distribution is performed in “real-time”, and the examination results are represented as color-coded images with the conventional B-mode image in the background (61). All subjects were evaluated with real-time elastography using a 9 MHz probe, through an intercostal space, with micrometer compressions, without having to apply great pressure. The measurement depth was 20 - 50mm (mean 35mm) with a 350-500mm² area of measurement (mean 420mm²) and ten valid measurements were performed. The investigators tried to find a new elasticity score, using a computer program specially developed using Matlab. This elasticity score ranged from 65 to 122. In this study, the comparison of histological liver fibrosis with RT-E showed a good correlation: increasing elasticity scores corresponding to increasing stages of fibrosis. The Spearman’s correlation coefficient between the elasticity score and the histological fibrosis stages was highly significant, with a value of 0.48 (p<0.001). The accuracy was 0.75 for significant fibrosis (F≥2), 0.73 for the diagnosis of severe fibrosis (F≥3) and 0.69 for the diagnosis of cirrhosis (F=4). In this study,
80% of patients with significant fibrosis (F≥2) could be correctly identified with RT-E and the elasticity score was not influenced by the degree of the steatosis in the liver. The conclusion of this study was that Hi Real-Time Elastography is a new and promising sonography-based noninvasive method for the assessment of liver fibrosis in patients with chronic viral hepatitis.

In a study performed by Fujimoto et al (66) on 43 patients with chronic C hepatitis and cirrhosis proven by means of LB, liver fibrosis assessment was also performed with a Hitachi EUB-8500 ultrasound machine, using a linear probe (6-13 MHz), by applying slight manual pressure while the subject briefly held the breath. The evaluation was blindly performed by six reviewers, in each subject. In this study it was shown that the assessment of liver elasticity score by RT-E may be influenced by the subjectivity of the evaluator, and that the accuracy would improve if the evaluator becomes accustomed with the procedure. The conclusion of this study is that RT-E satisfactorily reflects the degree of fibrosis.

In the study of Tatsumi and al (67), RT-E was performed in 119 patients with chronic liver disease and LB (HCV in 102 patients, HBV in 3, and non-B, non-C in 20), and compared to TE and serum fibrotic markers. A Hitachi EUB-8500 ultrasound machine with a linear probe (6-13 MHz) was used. In this study, tissue elasticity was calculated using real-time tissue elastography, in which numerical values from 0 to 255 (256 stepwise grading) were determined according to color mapping, from blue (0) to red (255). In a second time, the percentage of the blue area in a region of interest (ROI) was calculated. In this study, HiRT-E showed a negative correlation with fibrotic stages and FibroScan findings, suggesting that real-time tissue elastography is better than FibroScan, with fewer limitations. The authors considered that another advantage of this method is the fact that the system is preinstalled on ultrasound equipment and that HiRT-E is a novel and promising method to assess hepatic fibrosis which could, maybe, replace LB in the future.

By using dynamic hue histogram analysis, other authors were able to quantify the liver elasticity inside a defined ROI, located at the periphery of the right liver lobe (69). In this study, the correlation between the mean elasticity values calculated by hue histogram analysis on average images and the degree of histological fibrosis stage was statistically significant. But, they strongly suggest that the elastography ROI should also include the tissues surrounding the liver because this would probably increase the accuracy of the technique (70).

Another study (29) was unable to find a good correlation between HiRT-E and the liver elasticity.

Very recently, the German group (68), which published the first study using Hi RT-E in liver fibrosis (62), performed a validation study of their own elasticity score and of the elasticity
score developed in Japan and compared the results of HI-RTE with TE. They evaluated a cohort of 134 patients with chronic hepatitis histological evaluated (n=112) or proven liver cirrhosis (n=20) and showed that HiRT-E, in its present form, cannot replace transient elastography for noninvasive assessment of liver fibrosis.

So, considering these published studies, HiRT-E might be a promising method for the evaluation of liver fibrosis in chronic hepatopathies, but new methods of color code interpretation are needed in order to improve the accuracy.

Real-Time Elastography from Siemens, a very new method, uses a different technology (30). The system enables qualitative visual and/or quantitative measurements of the mechanical stiffness properties of the tissue. By eSie Touch™ elasticity imaging, high resolution elastography images are obtained, applying gentle compression. A real-time qualitative elastogram feedback assists the imagists in optimizing their acquisition technique. On the other hand, Virtual Touch™ tissue imaging application implements Acoustic Radiation Force Impulse (ARFI) technology for the evaluation of deep tissues, not accessible to superficial compression elastography techniques. Using image-based localization and a proprietary implementation of Acoustic Radiation Force Impulse (ARFI) technology, shear wave speed may be quantified in a precise anatomical region, focused on a region of interest, with a predefined size, provided by the system. Measurement value and depth are also reported.

Another advantage is the fact that ARFI measurement can be performed with software integrated into a conventional ultrasound machine, so that a screening ultrasound examination and elastography examination, can be performed with the same machine, while with TE only elastography can be performed.

**Acoustic Radiation Force Impulse (ARFI) technology**

ARFI imaging involves targeting an anatomic region, to be interrogated for elastic properties with use of a region of-interest cursor, while performing real-time B-mode imaging. Tissue, in the region of interest is mechanically excited, by using short-duration (262 µsec) acoustic pulses, with a fixed transmit frequency of 2.67 MHz to generate localized tissue displacements. The displacements result in shear-wave propagation away from the region of excitation and are tracked by using US correlation-based methods (71). The shear-wave
propagation velocity is proportional to the square root of tissue elasticity. Results are expressed in meters per second (m/s).

**Figure 6** ARFI measurement in a patient with liver cirrhosis.

In clinical scanning of the liver, it would be better that a scanning protocol to be followed-up according to Siemens recommendations: if the right lobe is intercostally scanned with normal breathing, the variance of measurement is low. It was observed that when the liver is scanned more medially and the patient is asked to take and hold a deep breath, combined with varying pressure applied with the probe against the liver to get a good image, there is more variability in the result. It is not known why, but there are theories that by compressing the liver, the stiffness may be increasing. Additionally, a breath hold will raise venous pressure, similar to what occurs in heart failure, known to increase the liver stiffness.

Generally, the best and most consistent results will occur when the "normal" state of the liver is measured. When scanning between the ribs (e.g. liver segment 8), no pressure is applied to the liver and you just ask the patient to stop breathing for a moment (instead of deep inspiration and breath hold).

In difficult patients, several measurement attempts are needed to “average” out the readings, with different patient positions sometimes required (like putting the patient in left lateral decubitus position to get better access to the liver, without excessive pushing or breath holds). In some patients, it may not be possible to get reliable readings. The user manual specification indicates a useable range of 0-3.2 m/s, with ±20% accuracy over the range. The lower the velocity, as in normal liver, the lower the variance of the estimated velocity value.

The producer recommendations for best results are to:
- Apply minimal scan pressure;
- Exclude data that varies significantly;
- Minimize breathing and avoid cardiac motion;
- Use the optimal window: intercostal right lobe (segment 8).

The factors that can affect measurement repeatability and reproducibility are:

- Excessive tissue motion (cardiac/breathing);
- Tissue attenuation;
- Poor scan window;
- Depth of ROI;
- Tissue stiffness;
- Local vessels/interfaces.

For clinical application with Virtual Touch Tissue Quantification scanning technique, the optimal sample location is in the right lobe, away from motion and portal/hepatic vessels. The left lobe should be avoided due to cardiac motion, as well as the subcostal approach and deep inspiration.

There are some studies regarding the evaluation of liver fibrosis by means of ARFI, showing encouraging results (30-34, 72).

In a study performed by Friedrich-Rust (30), in which ARFI was compared to LB and blood markers in 86 patients with chronic hepatitis (B or C), Spearman correlation coefficients between the histological fibrosis stage and ARFI, TE, FibroTest and APRI scores, indicated significant correlations: 0.71, 0.73, 0.66 and 0.45 respectively (p<0.001). The diagnostic accuracy of ARFI-imaging, TE and FibroTest were 0.82, 0.84, and 0.82, respectively, for the diagnosis of significant fibrosis, and 0.91, 0.91, and 0.82, respectively, for the diagnosis of liver cirrhosis.

In another study (72) that assessed the performance of ARFI evaluation in chronic hepatopathies and healthy volunteers, 114 subjects were included: 38 healthy volunteers, 53 patients who had undergone LB and 23 previously diagnosed with LC). In each patient, in the same day, LS measurement was performed by means of ARFI (by using a Siemens Acuson S2000™ ultrasound system) and by means of TE (FibroScan). Fifteen ARFI measurements were performed, 5 determinations in each of 3 positions: subcapsular, 1-2 cm and 2-3 cm under the liver capsule, respectively (median value of 5 measurements in each position). This study demonstrated a significant, direct correlation between ARFI and the severity of liver fibrosis (p<0.001). The correlation between ARFI and the severity of liver fibrosis was
rho=0.469 subcapsular, rho=0.675 and rho=0.714 respectively (p<0.001). The subcapsular measured values of ARFI showed a poor correlation with fibrosis. The AUROC analysis, regarding the whole group of patients (healthy volunteers, patients with LB and patients with proven cirrhosis), showed that the best test for predicting significant fibrosis (F≥2 Metavir) was TE, with AUROC 0.908, significantly larger than the AUROC’s for ARFI. If only ARFI is considered, measurements made 1-2 and 2-3 cm under the liver capsule have the best predictive value, with AUROC’s not significantly different from each other (0.767 and 0.731, respectively, p=0.264). The optimal cut-off value for predicting significant fibrosis (at least F2 Metavir) was obtained for ARFI measurements 2-3 cm under the liver capsule (1.26 m/s with 0.74 sensitivity and 0.67 specificity). For measurements made 1-2 cm under the liver capsule, the optimal cut-off value for significant fibrosis was 1.4 m/s with 0.70 sensitivity and 0.78 specificity.

In this study, the cut-off values of TE and ARFI measurements for predicting the presence of fibrosis (F>0) were: for TE - 5.65 kPa (AUROC-0.898) and for ARFI - 1.4 m/s for measurements made 1-2 cm under the capsule (AUROC-0.747) and 1.26 m/s for measurements made 2-3 cm under the capsule (AUROC-0.721). The cut-off values of TE and ARFI measurements for predicting cirrhosis (F=4 Metavir) were: for TE - 12.9 kPa (AUROC-0.994) and for ARFI - 1.8 m/s for measurements made 1-2 cm under the capsule (AUROC-0.929) and 1.78 m/s for measurements made 2-3 cm under the capsule (AUROC-0.951). This study also demonstrated (two-way ANOVA test) that, even if there are different values of ARFI measurements made 1-2 cm and 2-3 cm below the capsule, corresponding to each stage of fibrosis, they are not statistically significant different from each other (p>0.05). Also, according to this study, F0 could not be differentiated from F1, also F2 from F3, both in 1-2 cm and in 2-3 cm under the capsule measurements (p>0.05).

In the study performed by Lupsor and co-workers (33), 112 consecutive patients with chronic hepatitis C were evaluated through histology (Metavir score), ARFI and TE. In this study, ARFI was correlated with liver fibrosis (r=0.717, p<0.0001) and necroinflammatory activity (r=0.328, p<0.014), but not with steatosis (r=0.122, p=0.321). In this study there was a significant increase of ARFI values in parallel with the increase in fibrosis stage: 1.079±0.150 m/s (F0-F1), 1.504±0.895 m/s (F2), 1.520±0.575 m/s (F3), 2.552±0.782 m/s (F4), p<0.0001, but there was a certain degree of overlap between the consecutive stages F1-F2 (p=0.072) and F2-F3 (p=0.965). In this study the cut-off values (m/s) predictive for each fibrosis stage were: 1.19 (F≥1), 1.34 (F≥2), 1.61 (F≥3) and 2.00 (F4). Concerning the comparison between ARFI
and TE, this study found that the AUROCs were: 0.709 vs. 0.902, p=0.006 (F≥1), 0.851 vs. 0.941, p=0.022 (F≥2), 0.869 vs. 0.926, p=0.153 (F≥3) and 0.911 vs. 0.945, p=0.331 (F4).

The last two studies that we presented (33, 72) showed that there is a strong correlation between histological fibrosis and ARFI measurements, also that the best performances of this method are in the prediction of severe fibrosis and cirrhosis and ARFI is not better than TE for the evaluation of liver stiffness.

On the basis of the multiple published studies for the evaluation of liver stiffness with ultrasound waves: Transient Elastography, Real-time Elastography and Acoustic Radiation Force Impulse (ARFI) Elastography, we can conclude that in this moment, all these methods are very promising non-invasive tools for the evaluation of liver fibrosis. Further clinical studies and new technological developments can improve the results of these methods, making them a solution that can replace LB in the future.

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