Elastography of Diffuse Liver Disease - where are we now?

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Learning objectives

To become familiar with the various modalities currently available to quantify liver fibrosis.

To appreciate the advantages and limitations of each technique

To appreciate the clinical applications ultrasound elastography allows.

Background

Currently, liver biopsy to obtain histology is considered the 'gold standard' to quantify liver fibrosis. However, biopsy is as an invasive procedure with recognised risks, limitations and monetary costs. Complications may range from pain, to more unusual but serious complications such as intraperitoneal haemorrhage. Furthermore, there is potential for sampling errors given the heterogenous nature of fibrosis distribution and the small area sampled by a liver biopsy (approximately 1/50000th of total liver volume). Studies have shown these factors may lead to misdiagnosis in 25% and discordance in fibrosis staging in up 33% \(^1\). Recognition of these constraints has led to a search for a safe, reliable and inexpensive non-invasive technique to quantify liver fibrosis. While Imaging offers alternatives including MRI and CT for this purpose, it is ultrasound elastography that has gained the widest interest. Favourable qualities of ultrasound quantification include: lack of ionising radiation; comparatively, the examinations are relatively quick and inexpensive; and ease of accessibility.

When performing liver biopsy, two clinically relevant critical endpoints are sought: Firstly, the detection of significant fibrosis (F2/ I3) (Image 1 and 2) which is an indication for the commencement of antiviral treatment in chronic hepatitis B and C; and secondly, the presence of severe fibrosis (F3/ I5) or cirrhosis (F4/ I6) which prompts the monitoring of associated complications such as portal hypertension and hepatocellular carcinoma.

Images for this section:
**Fig. 1**: Metavir histological scoring system for the assessment of liver fibrosis

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**Fig. 2**: Ishak histological scoring system for the assessment of liver fibrosis.
Imaging findings OR Procedure details

The four most investigated modalities for US elastography assessment are: Transient elastography (TE), Real time tissue elastography (Hi-RTE), Acoustic radiation force impulse (ARFI) imaging and SuperSonic Imaging (SSI) (ShearWave elastography).

**Transient Elastography (Fibroscan™, Echosens, Paris, France)**

**Physics:**

An ultrasound probe is placed in the right intercostal space and when activated emits a low frequency elastic shear wave (50Mhz). Pulse echo acquisition is then performed to follow the shear wave and measure the velocity within a predetermined region of interest. The propagation velocity of a wave through tissue is proportional to its elasticity (stiffness); ie. the stiffer the liver, the faster the shear wave propagates.

**How to Perform:**

The ultrasound probe is placed within the right intercostal space over the liver and measures shear wave propagation in a 4cm x 1cm area (Figure 3). Values obtained which do not conform to the expected vibration shape or propagation are automatically rejected. The manufacturers have made three key recommendations: 1) At least 10 measurements are taken, (2) A success rate of 60% of measurements to be valid, (3) The ratio of the interquartile range and median value is lower than 0.3.

**Current Evidence:**

TE is the most widely analysed modality with the first report published in 2003. A number of meta-analyses have been performed, the most recent of which evaluated 40 studies and demonstrated a summary sensitivity of 0.83 (95% CI: 0.79-0.86) and a specificity of 0.89 (95% CI: 0.87-0.91) for the detection of F4 disease. The findings are comparable to a previous meta-analysis of nine studies that compared TE with liver biopsy. Cirrhosis detection with TE was associated with a pooled sensitivity of 87% (95% CI: 84-90%), specificity of 91% (95% CI: 89-92%) and Frederich-Rust et al. showed an overall accuracy of 0.94 (95% CI: 0.93-0.95) for the detection of cirrhosis and suggested an optimal cut-
of 13.0 kPa. Additionally, in the evaluation of chronic hepatitis C, several studies and meta-analyses have shown that values of liver stiffness between 6.8-7.6 kPa determine significant fibrosis (F>2). However, no study has, as of yet, determined accurate values for the individual stages of fibrosis.

**Advantages/Disadvantages:**

TE offers a number of advantages. Primarily, it is a non-invasive test and can be repeated at regular intervals in an outpatient setting. In addition, the test is relatively inexpensive and samples an area that is approximately 100 times greater than that of a biopsy.

There are a number of limitations of TE: there is no B-mode image for correlation or determination of a region of interest. Also, shear waves fail to propagate within fluid and hence patients with decompensated cirrhosis cannot be adequately assessed. Obese patients and those with metabolic syndrome may also be subject to unreliable assessment due to beam attenuation through soft tissues. Recent steps have been taken to overcome this by creating a 2.5MHz frequency probe.

**Clinical Applications:**

TE has been validated for hepatitis C and been incorporated into the European Association for the Study of the Liver (EASL) 2011 guidelines. Although liver biopsy is still the gold standard, TE can be used to assess the presence of significant fibrosis (F>2) and hence institute antiviral treatment. However, use is not recommended in patients whom are obese or with ascites present. Several authors have suggested the use of combined non-invasive tests (TE and serum markers) to improve diagnostic accuracy.

A potential use for TE would be in follow-up of patients treated with antiviral treatment, however, care must be taken in this setting, as improving values may be attributed to decreasing necro-inflammation rather than true resolution.

**Real Time Elastography (RTE), Hitachi Sonoelastography (Hi-RTE™)**

**Physics:**
RTE performed with the Hitachi system (EUB-8500 and EUB-900) was the first modality to appear for clinical evaluation. While there has been subsequent evolution of the technology, the premise is based on an ability to display local differences in tissue stiffness by calculating the strain response of the tissue to stress; achieved by comparing and analysing echo signals before and under slight operator induced compression. Hard tissue is less compressible and undergoes a lesser degree of phase displacement of the reflected echoes, in comparison to soft tissues.

By incorporating a high-speed algorithm Hitachi Medical systems were able to overcome initial problems of aliasing and phase displacement allowing for real time imaging. Following criticism of user variability due to manual compression, a system was developed that used the aortic or cardiac pulsation to provide the necessary compression in a more regulated manner.

How to Perform:

RTE incorporates direct correlation with B mode imaging and is performed through a standard transducer with an image overlay utilising a colour-coded scale from red (hard) to blue (soft). The region of interest can provide data for analysis in the form of a histogram for semi or full quantitative analysis.

Figure 4 demonstrates the image overlay of the real time elastography on the B mode imaging in (a) a normal healthy liver and (b) a fibrotic liver.

Current Evidence:

The initial study performed on Hi-RTE™ in liver disease demonstrated a diagnostic accuracy of 0.75\(^7\) for significant fibrosis. However, the study was later criticised for inherent inter-observer variability and the modality was deemed insufficient in its current form to replace TE. In response to the inherent inadequacies of assessment, Hitachi Medical systems developed a method in which aortic or cardiac pulsation replaced the need for external compression.

A study by Morikawa et al.\(^8\) created a binary image from the colour data and evaluated the mean strain, standard deviation, percentage hard area and complexity (complex ratio of the shape of an extracted hard tissue domain in the ROI) (figure 5). Results showed discrimination of stages of fibrosis (P<0.05) and the authors postulated that the mean and area may directly represent liver elasticity, while SD and complexity may imply the
collapse of the uniform architecture of the liver concomitant with progressing hepatic fibrosis. The results compared favourably with TE. A more recent study used semi-quantitative analysis using an elastic strain ratio, with the hepatic vein as a control ROI\(^9\). Analysis of the findings showed no significant inter-observer variability (ICC 0.966) and the AUROC curve was superior to that of serum markers for fibrosis. A further study by Wang et al.\(^{10}\) used direct quantification via 11 parameters to comprise a elasticity index (using a HI VISION Preirus, 5MHz probe). A strong correlation was found between stage of fibrosis and the new quantitative index. Furthermore the results of RTE outperformed that of APRI (a serological marker).

Advantages/Disadvantages:

HI-RTE\(^{TM}\) confers several benefits over TE, namely, real-time imaging and direct correlation between elastographic images and anatomical B-mode images. Additionally the integration of hardware allows easy access to immediate elastographic evaluation at the time of routine ultrasound imaging. The development of HI-RTE\(^{TM}\) has meant that aortic or cardiac pulsation can be used rather than external compression. As a result, this technique can be used in those with ascities unlike TE.

Although promising, more studies are required to evaluate the use of HI-RTE\(^{TM}\) in diffuse liver disease with the aim of a more quantitative and uniform method of assessment.

Clinical Applications:

Although HI-RTE\(^{TM}\) has already been proven effective in evaluation of lesions in the breast, thyroid and prostate there is a paucity of data surrounding diffuse liver disease. Studies have suggested the use in hepatitis C for evaluation of fibrosis and combination with serum markers may provide an alternative to biopsy. However, uniform image acquisition and data analysis needs to be determined in order to achieve a full validation of the technique.

Acoustic Radiation Force Impulse (ARFI) Imaging (Virtual Touch\(^{TM}\); Siemens).

Physics:
ARFI involves the generation of short duration acoustic pulses at a fixed frequency of 2.67Mhz. These pulses are directed towards a standardised region of interest (ROI). Subsequent displacement of the tissue within the ROI generates a shear wave propagation (Figure 6). The velocity of the propagation is then measured and quantified. The premise of ARFI is based on stiffer livers generating higher shear wave velocities.

**How to Perform:**

B-mode standard ultrasonography and quantitative ARFI measurements are carried out using a Siemens Acuson S2000 (Siemens), equipped with a 4C1 transducer. Tissue stiffness analysis is performed using the 'Virtual Touch\textsuperscript{TM}' (Siemens), quantitative imaging application. This calculates a numerical measurement (shear wave velocity), in metres/second, for the selected ROI tissue, using a standardized ROI box (fixed dimensions of 1.0 cm x 0.6 cm). It is recommended that the right lobe is scanned intercostally without undue pressure to the transducer. By scanning more medially, the unwanted effects of cardiac pulsation are encountered and results are shown to be unreliable. The manufacturers recommend a total of 10 readings should be obtained with avoidance of any visible vascular or biliary structures, targeting solely the liver parenchyma. When no valid measurement is attainable, the software returns a 'XXXX' symbol on the screen. In a study published in 2011\textsuperscript{11}, the optimal place for ARFI measurements was evaluated. The best correlation with histological fibrosis was observed for measurements made 1 - 2 cm and 2 - 3 cm under the liver capsule, and in further studies has been shown to be effective when measured as deep as possible\textsuperscript{12}. An example of an optimal location is shown in Figure 7.

**Current Evidence:**

A study in 2009\textsuperscript{13} evaluated ARFI in comparison to TE and serological markers of fibrosis in patients with chronic hepatitis B or C. ARFI was found to have a diagnostic accuracy of 0.82 for the detection of significant fibrosis and was comparable to TE. Sporea et al replicated these findings and demonstrated a diagnostic accuracy of 0.880, 0.893, 0.908 and 0.937 for stages (F\textsuperscript{>1}, F\textsuperscript{>2}, F\textsuperscript{>3}, F\textsuperscript{>4} respectively) using ARFI. A culmination of nine ARFI studies was reviewed in a meta-analysis by Freidrich-Rust\textsuperscript{14} using liver biopsy as a gold standard. It was found that ARFI had an accuracy of 0.87 for the detection of significant fibrosis (F\textsuperscript{>2}) and 0.93 for cirrhosis (F4). Furthermore, a subset of patients undergoing TE and ARFI showed comparable values for cirrhosis. Another study\textsuperscript{15}, which investigated 122 patients, found ARFI measurement values in cirrhotic patients were significantly higher than the other patients within the group (P, 0.001). Rate of invalid measurements was lower in ARFI than in Fibroscan\textsuperscript{TM} (P, 0.04). Both elastography methods were highly correlated to each other (P, 0.001). Furthermore, ARFI correlated
to histological grading of liver fibrosis (P, 0.001) and to inflammatory activity (P, 0.05). Liver steatosis had no statistical influence on ARFI results in contrast to Fibroscan™ (P, 0.05). A study of 112 with chronic hepatitis C patients compared TE and ARFI with liver biopsy. At the fibrosis stage (F≥3 and F≥4) ARFI was comparable to TE, however at F≥1 and F≥2 TE outperformed ARFI.

The various studies highlight the emergence of ARFI in the non-invasive evaluation of liver fibrosis and cirrhosis but not for lower grades. Although promising, it appears the technology is on a learning curve, as is the case with any innovation. As such, further studies are required to fully evaluate its efficacy.

Advantages/Disadvantages:

ARFI confers several advantages over TE, in particular is the benefit of being able to measure deeper within the liver parenchyma and obtaining B-Mode images. Furthermore, propagation of the shear wave is not affected by the presence of ascites or obesity.

There remains a void in the correct evaluation of lesser stages of fibrosis. With no absolute cut-off values defined for stages of fibrosis, further larger studies are needed to clarify its utility.

Clinical Applications:

Large multi-centre trials are needed to assess ARFI further, however as it shows reproducibility and results comparable to TE, there is promise. Preliminary studies have evaluated the use of ARFI in the follow up of viral hepatitis in small studies and showed reduction in ARFI values with sustained virological response and may represent a future utility.

Supersonic Shear Imaging (SSI), ShearWave Elastography

Physics:

SSI is the most recent development in elastographic imaging and provides real time imaging of local viscoelastographic properties. Acoustic radiation force is used to remotely generate low frequency shear waves at supersonic speed. The high-speed
production means successively deeper levels can be focused upon. Using ultrafast image acquisition, frame rates of a few thousands images per second are acquired, 100 times faster than the frame rates due to parallel processing (Figure 8). The result is real time elastography images on a B-mode overlay with improved spatial resolution to approximately 1mm. The improvement in spatial resolution has provided far greater diagnostic accuracy and can be seen in Figure 9, where the use of SSI reveals previously unseen internal variation in elastography of a lesion.

How to Perform:

SSI is incorporated into a standard transducer. The rapid acquisition of data also allows for elastographic analysis over a large volume. The size and position of the SWE image is user adjustable, enabling a tradeoff in frame rate and extent of view. By placing a circular region of interest (ROI) in a SWE image, the mean and standard deviation (SD) of the elasticity within the ROI can be displayed.

Current Evidence:

An initial study compared SSI, TE, serological markers and liver biopsy in 104 patients with chronic hepatitis\(^{17}\). Findings revealed 0.9 and 0.91, sensitivity and specificity for F4 with SSI. Ferrarioli\(^{18}\) recently conducted a small study which showed AUROC values were: 0.91 for F # 2; 0.99 for F # 3 and 0.97 for F = 4 and that SSI was comparable to TE. This was followed by a larger study of 113 patients performed in hepatitis C patients, which produced similar results. SSI correlated with fibrosis stage (p<0.0001) and AUROC of 0.948 for F # 2, 0.962 for F # 3 and 0.968 for F = 4. SSI AUROC values were also found to favourable when compared to TE\(^{19}\).

Advantages/Disadvantages:

SSI offers a new step in viscoelastographic imaging with ultrafast acquisition of data and deep level focussing. The result is true realtime elastography, with improved spatial resolution compared to prior techniques. The early studies seem to suggest better evaluation of low grade fibrosis compared to TE and ARFI, however there is a clear lack of substantive evidence and definitive larger studies are needed.

Clinical Applications:
Currently there are only a small number of studies on SSI but the results are promising, especially for the lesser stages of fibrosis.

**Images for this section:**

![The METAVIR Fibrosis Staging System](image)

**Fig. 1:** Metavir histological scoring system for the assessment of liver fibrosis
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**Fig. 2:** Ishak histological scoring system for the assessment of liver fibrosis.

![Ishak histological scoring system](image)

**Fig. 3:** TE imaging with depiction of ROI within the liver parenchyma.

![TE imaging with ROI](image)
Fig. 4: Image overlay of the real time elastography on the B mode imaging in (a) a normal healthy liver and (b) a fibrotic liver.
Fig. 5: Hi-RTE histogram obtained for subsequent analysis
Fig. 6: Schematic illustration of acoustic radiation force impulse measurement acquisition.
**Fig. 7:** Realtime acoustic radiation force impulse measurement in a healthy volunteer. The region-of-interest (ROI) box (overlying parenchyma) is the focus for measurement. The displayed depth (cm) from the skin surface and shear wave velocity measurement (m/s) is displayed on the right of the image.
The key concept of ultrafast Imaging is plane wave transmission

Conventional Imaging

Ultrafast Imaging

128 to 512 transmits for a full image
(typically 10 to 50 ms)

1 single transmit for a full image
(typically 100 to 500 μs)


Fig. 8
True assessment of tissue stiffness
Hard lesion with a liquid center

Fig. 9
Conclusion

There is potential for replacing invasive methods of evaluation with non-invasive modalities. There has been significant progression in elastography and all four modalities appear promising for the evaluation of liver fibrosis. To further the development, it would seem certain issues need consideration:

(i) The inherent inadequacies of the 'reference standard' of liver biopsy need to be addressed.

(ii) A universal protocol for image acquisition.

(iii) Prospective validation of cut-off values.

The advent of elastography is exciting, both in its application and in its potential benefit for the patient. However, further studies are needed - particularly involving SSI. Utilisation of these techniques has already led to a reduction in the need for biopsy. It appears ultimately an integrated algorithm as an endpoint will allow a more streamlined and convenient patient experience.

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