ShearWave™ Elastography Improves the Assessment of Liver Fibrosis

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A number of different insults to the liver result in liver fibrosis. Viral, autoimmune hereditary, metabolic and toxin-mediated affronts all can lead to a progression of liver injury ending finally in liver cirrhosis. The prognosis and clinical management of chronic liver diseases are highly dependent on the extent of liver fibrosis. At present, liver biopsy (LB) is the standard examination for the assessment of liver fibrosis. However, it is an invasive method with several limitations. The invasive aspect is associated with patient discomfort and in rare cases (from 1/4,000 to 1/10,000) with serious complications. In addition, the accuracy of LB is limited due to sampling error and significant intra- and inter-observer variability in histological staging. Given these limitations, LB is not ideal for liver stiffness assessment, and especially for repeated assessment of disease progression. Both the progression and the regression of liver fibrosis over time could be of clinical significance. Recent research has demonstrated reduction in liver fibrosis with treatment even in advanced stages.

These limitations of LB have motivated research for non-invasive methods of measuring liver fibrosis. Transient elastography (TE) has emerged as the non-invasive test of reference and is entering clinical practice in Europe. TE is a non-invasive method that evaluates liver stiffness by measuring the velocity of elastic shear waves in the liver parenchyma generated by a mechanical pulse. Several studies have shown significant positive correlation between TE and the stage of liver fibrosis. Therefore, TE has shown potential utility in assessing the level of liver fibrosis, but also in following-up liver fibrosis, after liver transplantation, anti-viral treatment or in cases of recurrence of HCV.

Strain imaging is commonly found on high-end ultrasound equipment, however most manufacturers use probe-induced or indigenous (respiratory or cardiac) displacements to generate qualitative images of strain. As the stress over the medium is unknown, a quantifiable estimate of tissue stiffness cannot be obtained.

ShearWave™ Elastography (SWE™) is also based on shear waves, and has been implemented on a diagnostic ultrasound system. Like TE, SWE estimates the propagation speed of a shear wave to provide a value of tissue stiffness. Additionally, SWE has the advantage of being able to image liver anatomy in real-time, while providing a real time map of stiffness. This method could result in a more accurate staging of fibrosis, due to the combination of SWE and B mode imaging. This paper describes the use of SWE for the assessment of fibrosis and presents early results of a clinical trial that have been published.
from the average of a circular ROI, 2 cm in diameter, when scanning conditions permitted. The mean value of four consecutive measurements was used for statistical analyses.

**TE Acquisitions**

TE was performed using FibroScan® (Echosens™, Paris, France). Measurements of liver stiffness were performed on the right lobe of the liver through intercostal spaces, following the examination procedure previously described\(^{20}\). A successful acquisition consisted of 10 validated measurements and an interquartile range (IQR) of less than 30% of the median liver stiffness value.

**Liver biopsy and histology**

Ultrasound-assisted percutaneous LB was performed in the same intercostal space as used for TE and SWE measurements. The specimens were read on site by a single expert liver pathologist (B.D.B.), blind to the results of both TE and real-time SWE results, but not to the patients’ clinical and biochemical data. Fibrosis was evaluated semi-quantitatively and staged on a five-point scale from 0 to 4 according to the METAVIR scoring system.

**Results**

Liver stiffness measurements were successful with both techniques in 118/121 (97.5%) of patients recruited. No patients with overt cirrhosis or ascites were recruited in this series of patients. The failed measurements were due to obesity (in 1 patient) and narrow intercostal spaces (in 2 patients). The resulting elasticity measurements in successful patients are reported in Table 1, grouped by METAVIR stage of fibrosis. The differences of elasticity values measures for F0-F1 and F2 METAVIR stages were highly significant, as between F2 and F3 stages. On the contrary, the differences in values measured for F3 and F4 were not significant, probably due to the limited number of patients with F3 (only 14 patients).

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**Table 1. Median values, interquartile ranges (IQR) of measurements, and p values for differences*, obtained for each fibrosis stage with SWE and TE.**

<table>
<thead>
<tr>
<th>Method</th>
<th>F0-F1</th>
<th>F≥2</th>
<th>F≥3</th>
<th>F=4</th>
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<tbody>
<tr>
<td>SWE</td>
<td>6.2 kPa [5.1-6.8]</td>
<td>7.6 kPa [7.2-8.3]</td>
<td>10.0 kPa [9.2-10.1]</td>
<td>15.6 kPa [12.8-18.8]</td>
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<tr>
<td></td>
<td>0.0001(^a)</td>
<td>0.003(^b)</td>
<td>0.09(^c)</td>
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<td>TE</td>
<td>5.3 kPa [4.5-6.4]</td>
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<td>19.8 kPa [13.4-23.0]</td>
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<td></td>
<td>0.02(^a)</td>
<td>0.002(^b)</td>
<td>0.06(^c)</td>
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</table>

\(^*\) p values of Kruskal-Wallis’ one-way analysis of variance by ranks to test differences between SWE and TE among fibrosis stages; \(^a\): F0-F1 versus F2; \(^b\): F2 versus F3; \(^c\): F3 versus F4.

The results of the ROC analysis for the detection of significant fibrosis (METAVIR F≥2), severe fibrosis (METAVIR F≥3), and cirrhosis (METAVIR F=4) are reported in Table 2. A significant improvement (p=0.002) in the area under the ROC curve (AUROC) for METAVIR F≥2 was observed between real-time SWE (0.92) and TE (0.84). The optimal cutoffs for SWE, obtained by ROC analysis, were 7.1 kPa (1.5 m/s), 8.7 kPa (1.7 m/s) and 10.4 kPa (1.9 m/s) for the detection of METAVIR F≥2, F≥3 and F4, respectively. The slight improvements for the AUROCs for severe fibrosis and cirrhosis were not statistically significant (p=0.14 and p=0.48 respectively).
Examples of SWE™ acquisitions for F0 and F4 stage of fibrosis from different patients are presented in Figures 1a and 1b respectively. The elasticity map is superimposed over a corresponding B-mode image. The placement of the ROI is facilitated by the B-mode and SWE images, to ensure a uniform region of tissue is selected for measurement.

Table 2.
Areas under the ROC curves (AUROC) of both SWE and TE as determined by ROC analysis, corresponding optimal cut-off values, and corresponding detection performances.

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<th>F≥2</th>
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<th>F≥3</th>
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<th>F=4</th>
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Discussion

Numerous non-invasive approaches have been developed and evaluated to stage liver fibrosis in the last decade including TE, and different MR and ultrasound techniques. Only TE has successfully entered clinical practice, particularly in a number of European countries. However, there is considerable variation in the performances reported for TE to predict significant fibrosis (AUROCs of 0.75 to 0.91)\textsuperscript{5-13}. TE is also hindered by the number of non-interpretable measurements, reaching nearly 20% of cases\textsuperscript{21}. The majority of non-interpretable TE exams originate from variability within the acquisitions comprising a final liver stiffness measurement (LSM). The prognosis and management of Hepatitis C patients strongly rely on the degree of liver fibrosis. Anti-viral treatment is usually initiated promptly in patients with advanced fibrosis (METAVIR score F3-F4), and is carefully considered for patients with significant fibrosis (METAVIR score F2)\textsuperscript{2}. In this study, real-time SWE\textsuperscript{TM} exhibited a significantly higher ability to identify intermediate stages of fibrosis in comparison with TE. The AUROCs in differentiating no/mild fibrosis (F0-F1) from significant fibrosis (F>2) were 0.84 and 0.92 for TE and real-time SWE respectively (p≤0.01). The performances of real-time SWE in identifying severe fibrosis (F≥3) and cirrhosis (F4) were similar to that of TE (0.98 vs 0.96 respectively for severe fibrosis, and 0.98 vs 0.96 respectively for cirrhosis), which were already quite high. These findings suggest that real-time SWE can be used similarly as TE is being used for the assessment of severe fibrosis and cirrhosis, with the benefit of improved assessment of significant fibrosis.

Real-time SWE has at least two advantages with respect to TE. Firstly, real-time SWE is integrated into a conventional diagnostic ultrasound system and, therefore, can make use of real-time B-mode imaging for the assessment of morphologic changes or detection of focal liver lesions (eg. hepatocellular carcinoma). The use of the B mode image for the guidance of SWE acquisitions also seems to reduce variability of liver stiffness measurements\textsuperscript{22,23}. Secondly, SWE provides a real-time two-dimensional quantitative map of liver tissue stiffness. This real-time aspect of SWE acquisition enables user adjustment during acquisition for targeting a homogenous region of liver tissue, and it also ensures that excessive liver motion is avoided. The spatial heterogeneity of liver stiffness can be visualized and the size of the region used for a measurement can be selectively placed or adjusted in order to avoid artifacts, such as those arising around larger pulsating vessels. As a result, physiological variations of liver fibrosis can be averaged out. Noteworthy, the volume of liver tissue sampled by one SWE acquisition is several hundred times larger than the one sampled by a biopsy core. Preliminary work suggests that real-time SWE should benefit from improved separation of fibrosis stages, due to the use of shear waves with greater bandwidths\textsuperscript{24}.

Conclusion

This study demonstrates that real-time ShearWave\textsuperscript{TM} Elastography (SWE\textsuperscript{TM}) can be used clinically to measure liver stiffness, with the guidance of the gray scale image. We also proved that SWE had surpassed TE in identifying the early stage of significant fibrosis, while it compared similarly with TE in staging severe liver fibrosis and cirrhosis. This suggests that SWE could be used as an additional tool for the non-invasive assessment of liver fibrosis, with advantages in acquisition and performance over TE. Further studies in larger patient populations are needed to confirm these results.
References


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