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Elastography for Detecting Hepatic Fibrosis: Options and Considerations

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The elasticity of human liver varies by several orders of magnitude when measured by ex vivo stress-strain experiments. In the presence of acute injury, the liver may display contractile properties related to the activation of cellular elements including myofibroblasts.¹ Emerging data further suggest that increased liver stiffness occurs even before collagen deposition takes place,² implying that tissue stiffness is a prerequisite for injury responses such as stellate cell activation. With the development of chronic liver disease, however, the increased stiffness observed in vivo is primarily dictated by the presence of fibrosis.³

Conventional medical imaging modalities have been developed to detect changes over much smaller ranges.⁴ In the past decade, several investigative groups have developed methods for imaging tissue elasticity, recognizing the incremental diagnostic value of characterizing mechanical properties when assessing for the presence of disease. Proposed techniques using ultrasonography or magnetic resonance (MR) platforms employ methods consistent with classical approaches where stress is applied to tissue and the resulting strain distribution is measured.

Transient elastography (FibroScan, Echosens, Paris, France) utilizes an ultrasound transducer probe mounted on the axis of a vibrator. Low-frequency (50 Hz) vibrations are transmitted into the skin by manual placement of the probe between the rib interspace where biopsy would be performed, inducing a shear wave that propagates into the liver. A pulse-echo acquisition is then used to measure the propagating wave's velocity, which is proportional to tissue stiffness represented by the equation for Young's elastic modulus E (expressed as $E = 3\rho v^2$, where v is the shear velocity and ρ is the density of tissue, assumed to be constant). Dedicated, machine-based software determines whether each measurement (quantified in units of kiloPascals) is successful or not. Requirements for accurate calculations of average liver stiffness include (1) an interquartile range for measurements within 30% of the median value and (2) a ratio of successful measurements to the total number of acquisitions 60%.⁵

Magnetic resonance elastography (MRE) directly visualizes and quantitatively measures propagating acoustic shear waves progressing through liver tissue.⁶ By using an electromagnetic or passive pneumatic driver placed directly on the patient for longitudinal shear wave generation, a phase-contrast magnetic resonance imaging pulse sequence detects the shear wave displacement patterns that are observed. Subsequently, the shear stiffness values are calculated from wave displacement patterns and displayed as color-encoded images (elastograms) that depict tissue elasticity. At our institution, region of interest analysis throughout 4 cross-sectional slices of liver (avoiding vascular structures) is

performed to calculate mean liver stiffness. Elasticity quantification by MRE is based on the formula representing shear modulus, which is equivalent to one third of the Young's modulus reported with transient elastography.^{7,8} MRE is operator independent in terms of generating wave propagation and is compatible with many phased-array torso coils, offering the possibility of multimodal hepatic imaging, including perfusion assessment.

The results of individual and combined results from clinical investigations of transient elastography demonstrate high sensitivity (>85%) and specificity (>90%) for detecting advanced hepatic fibrosis in patients with chronic hepatitis C.⁹ Single-center studies with MRE have also reported high degrees of accuracy for detecting advanced fibrosis in patients with various disease etiologies as well. Furthermore, the expanded application of MRE is noted for detecting stages 2–4 hepatic fibrosis with sensitivity and specificity values in the 85%–90% range, respectively.^{7,8} Because both technologies are likely to become available in the United States in the near future, a direct comparison between modalities to assess performance and clinical utility will be inevitable.

In this month's issue of *GASTROENTEROLOGY*, Huwart et al¹⁰ report on 141 patients who underwent blinded assessments with transient elastography, MRE, and aspartate aminotransferase to platelet ratio index (APRI) after liver biopsy to assess which method could most accurately predict the degree of hepatic fibrosis. Individual patients underwent both imaging examinations and it was noted that the technical success rate for MRE was significantly higher than for transient elastography (94% vs 84%). Reasons for incomplete transient elastography included the presence of minimal ascites ($n = 13$) and obesity ($n = 10$), defined as a body mass index ≥ 28 kg/m². Incomplete MRE studies were related to claustrophobia, inability to enter the MR scanner owing to body habitus, and low hepatic signal from elevated hepatic iron content. Of the 96 patients with suitable results from noninvasive fibrosis examinations and liver biopsy, nearly 65% had chronic hepatitis C and the average body mass index was 26 kg/m². The distribution of fibrosis on liver histology was stage 0, 23%; 1, 23%; 2, 20%; 3, 15%; and 4, 19%, with a mean specimen length of 30 mm.

The authors report that all 3 noninvasive modalities provided measurements that correlated with fibrosis stage, but the strongest relationship was observed with MRE ($r = 0.84$; $P < .001$). The diagnostic performance of MRE was also greater than transient elastography and APRI for the detection of fibrosis stages 2–4 vs stages 0–1 based on receiver operating characteristic curve analyses. Notably, the sensitivity and specificity for detecting stages 2–4 hepatic fibrosis by MRE were 100% and 91%, respectively. Finally, the performance of MRE in detecting hepatic fibrosis remained higher when compared to the combination of transient elastography and APRI.

Advantages of the reported study design include (1) the use of consecutive patients for identifying study participants, (2) blinding of all test strategy results to interpreters, (3) a high frequency of suitable liver histology specimens, which minimized sampling error, (4) excellent interobserver hepatopathologist reproducibility for staging fibrosis, and (5) the use of advanced statistical methods for examining diagnostic performance. Potential limitations of the investigation include (1) the exclusion of patients with unsuitable liver biopsies and imaging study results, which could result in bias toward higher performance rates and (2) the inability to successfully examine greater numbers of patients with obesity (only 12% with body mass index ≥ 28 kg/m²) and nonalcoholic fatty liver disease with transient elastography.

Although the underlying principles for both transient elastography and MRE seem similar, there are key differences in these methods that should be considered when interpreting the

results they produce. Specific issues are related to the concepts of reproducibility, accuracy, and fibrosis stage misclassification.

Reproducibility

The inter- and intraobserver reproducibility of transient elastography in studies focused on defining this aspect of performance is considered excellent, measured by an intraclass correlation coefficient (ICC) of 0.98.^{11,12} Reductions in the degree of agreement, however, are noted when patients with early stage hepatic fibrosis, 25% hepatic steatosis on liver histology, and body mass index ≥ 25 kg/m² are examined. Although the reproducibility of MRE is similar with ICC values of 0.97 in this study,¹⁰ these results are largely unaffected by the variables described above. In fact, we have observed similar reproducibility values with MRE in patients with substantially higher degrees of hepatic steatosis and body mass indices (unpublished data). Among populations consisting primarily of lean individuals (body mass index <28 kg/m²), the incomplete examination rate for transient elastography may be as high as 10%. Notably, it is likely that even higher rates of incomplete examinations will occur within medical practice settings throughout North America, where obesity is highly prevalent. For MRE, there have been few limitations for performance related to body mass index or distribution of truncal obesity, exemplified by successful imaging even among patients with body mass index values >40 kg/m².⁸

Accuracy

Transient elastography is designed to measure liver stiffness in a cylindrical-shaped area 1 cm wide and 4 cm long confined exclusively to the peripheral right liver (Figure 1). Although the area of measurement is at least 100 times larger than a typical liver biopsy specimen, this still remains only a fractional component of the total hepatic parenchymal area. In turn, the presence of residual sampling error with transient elastography could be a factor in determining its accuracy. In the current study, Huwart et al report a higher than expected accuracy for transient elastography in detecting advanced fibrosis based on several components including the use of highly trained operators (reflected in the consistent, narrow inter-quartile ranges across all fibrosis stages), availability of large high-quality biopsy specimens for staging fibrosis, and the exclusive study of lean patients (88% of cases with BMI <28). Despite these conditions, the detection of stages 2 – 4 fibrosis remained less accurate when compared with values measured by MRE. This observation is likely related to the spatial heterogeneity of fibrosis deposition within the liver even with earlier stages of disease. Furthermore, MRE has the ability to calculate liver stiffness over entire hepatic cross-sectional areas from multiple slices throughout the parenchyma, which captures the impact of spatial heterogeneity in determining average liver stiffness values (Figure 1). We believe this explains, in part, the higher sensitivity and specificity values reported for MRE in detecting both clinically important hepatic fibrosis (stage 2) as well as cirrhosis.^{7,8,10}

Misclassification of Fibrosis Stage

Misclassification of fibrosis stage by elastography techniques is based on 2 factors. The ability to correctly discriminate between stages 0, 1, or 2 hepatic fibrosis rests on factors associated with liver biopsy quality (specimen length, number of portal tracts for assessment)¹¹ as well as spatial distribution of fibrosis for an individual patient. For example, patients with stage 1 fibrosis on liver histology may have elasticity values corresponding to either stage 0 or 2 fibrosis. In contrast, it is much more common to identify liver stiffness values compatible with cirrhosis among individuals when liver histology reveals stage 3 fibrosis. This suggests the influence of biopsy fragmentation and the variable acquisition of regenerative nodules in liver tissue to provide a definitive diagnosis of histologic cirrhosis. Overall, the misclassification rate (by 1 stage) observed by Huwart et al

was 25% with two thirds of cases having stages 0–2 on liver histology. Notably, there were no patients with cirrhosis who were misclassified with lower than expected mean liver stiffness values. In contrast, the misclassification rate for patients with cirrhosis alone is reported at 8% with transient elastography.¹² Of note, Huwart et al failed to observe an association between liver tissue specimen length (categorized in tertiles) and MRE result to explain the observed misclassification results. Although statistical analysis was performed to identify whether various combinations of imaging and serum tests were more accurate than single modalities alone, the “stepwise” use of MRE in a protocolized algorithm and its performance in this setting awaits further study.

Over the last year, MRE has made its way from the laboratory to the clinical practice. We have performed >450 MRE examinations to date among patients referred directly from ambulatory and hospital-based care settings. Furthermore, the high negative predictive value of MRE for detecting advanced fibrosis has allowed for a systematic approach to determine which patients would benefit most from liver biopsy referral. Results to date support the observation that a normal mean liver stiffness value by MRE in the setting of chronic liver disease is also consistent with stage 0 fibrosis on liver biopsy (unpublished data). Ultimately, cost-effectiveness and available expertise (especially in community-based settings) will play important roles in determining the clinical utility for any elastography-based technology used for detecting hepatic fibrosis. The future of elastography imaging is bright, with the next frontier comprising aspects of longitudinal assessment to link the quantitative measurement of liver stiffness with clinical outcomes including fibrosis progression, prognosis, and response to therapeutic interventions.

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Figure 1. Representative areas of hepatic parenchyma examined by transient elastography (*left panel*) and MRE (*right panel*) for detecting stage of hepatic fibrosis. A larger region of interest is available for calculating mean liver stiffness with MRE.