

## Noninvasive Assessment of Liver Fibrosis and Portal Hypertension With Transient Elastography

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**Hepatic fibrogenesis, the “final” common result of injury to the liver, is believed to be a critical factor leading to hepatic dysfunction and may be important in the pathogenesis of portal hypertension. Thus, accurate assessment of the degree of fibrosis is important clinically. For many years, examination of hepatic histopathology has been considered to be the “gold standard” tool used to assess fibrosis. However, liver biopsy is invasive, and in many instances not favored by patients or physicians. Thus, alternative approaches to measure liver fibrosis would be extremely attractive. To the extent that transient elastography is able to measure “liver stiffness,” which is proportional to the degree of liver fibrosis, this technique holds great promise.**

Hepatic fibrosis is the final result of a wide variety of types of liver injury. Fibrosis is a wound healing response, which is similar mechanistically to that observed in essentially all organs.<sup>1</sup> One of the most remarkable aspects of the wounding response in the liver (and in all tissues) is enhanced extracellular matrix production, or fibrogenesis. Injury-induced fibrogenesis is characterized by a multifold increase in interstitial collagens such as type I and type III, and many other extracellular matrix constituents.

Hepatic wounding is an integrated response, involving many cellular, biochemical, and molecular events (Figure 1). A critical feature is the transformation of resident stellate cells (also lipocytes, Ito cells, or perisinusoidal cells) from the *quiescent* to the *activated* state (Figure 1).<sup>2</sup> Among the most prominent functional changes associated with activation is a striking increase in secretion of extracellular matrix proteins,<sup>3</sup> presumably responsible for the overall fibrogenic response. Several other cell types, including bone marrow-derived precursors, portal fibroblasts, and perhaps others, may also play a role in fibrogenesis.

### The Relationship of Fibrosis and Portal Hypertension: Pathophysiology

Elevated portal pressure resulting from liver injury has been postulated to include elements of increased intrahepatic resistance as well as increased flow through the splanchnic system (eg, a hyperdynamic circulation). Increased intrahepatic resistance is an early and consis-

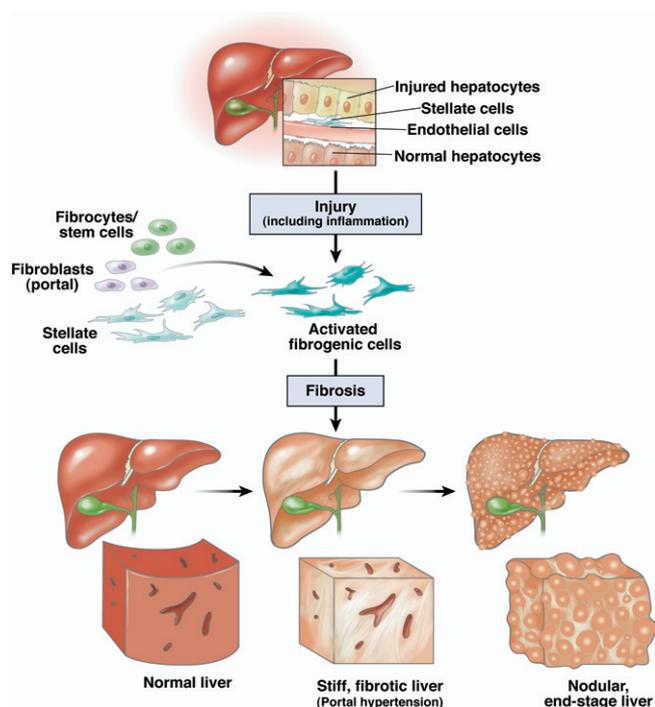
tent feature of liver injury; potential causes include impaired blood flow owing to regenerative nodules, intrahepatic shunts, hepatocyte swelling, extinction of typical vascular units after cycles of injury/repair, and perisinusoidal constriction. The latter mechanism has been proposed to be due to stellate cells, which also morphologically resemble tissue pericytes, a smooth muscle–like cell that regulates blood flow via pericapillary constriction.<sup>4</sup>

An additional feature of stellate cell activation is the *de novo* expression of smooth muscle–specific proteins, including smooth muscle  $\alpha$  actin,<sup>5</sup> presumably imparting an exaggerated contractile phenotype on stellate cells,<sup>6,7</sup> consistent with enhanced perisinusoidal constriction and increased intrahepatic resistance.<sup>7</sup> Furthermore, stellate cells respond to a number of “vasoactive peptides.”<sup>8</sup> Therefore, stellate cell activation leads to both fibrosis and contractility, raising the possibility that the processes may be linked. Furthermore, in the context of emerging data emphasizing endothelial dysfunction after liver injury, there is a compelling pathophysiologic basis for increased intrahepatic resistance typical of early forms of liver injury.<sup>9</sup>

### Why Is Quantitation of Fibrosis Important?

Precise measurement of the fibrotic lesion is important for several reasons. First, progressive fibrosis is believed to predict progression to cirrhosis in patients with hepatitis C virus (HCV) infection<sup>10</sup> and other diseases.<sup>2</sup> Additionally, the fibrosis stage may predict the likelihood of response to interferon-based antiviral therapy in patients with HCV; for example, patients with F3 or F4 fibrosis typically have a lower response rate to therapy.<sup>11</sup> Finally, therapy may be intentionally withheld in patients with minimal fibrosis or slow progression.

Data suggesting a relationship between fibrosis and outcome are emerging. In 116 patients with HCV infection undergoing liver biopsy (and hepatic venous pressure gradient [HVPG] measurement) after liver transplantation, a METAVIR fibrosis score of >F2 predicted clinical decompensation (AUC: 0.80).<sup>12</sup> In a long-term cohort study of 160 patients with primary biliary cirrho-



**Figure 1.** Hepatic fibrogenesis. In most diseases leading to fibrosis, injury, and subsequent inflammation are prominent. Injury, typically involving epithelial cells (hepatocytes in the liver), leads to activation of immune cells and an inflammatory response. Inflammatory mediators, but also changes in the extracellular milieu, are an important stimulus for stellate cell activation and thus fibrogenesis. Importantly, once activated, the stellate cell activation arm becomes self-perpetuating via various autocrine systems. Although stellate cells appear to be the most critical effectors of fibrogenesis, other cell types (portal fibroblasts, fibrocytes), also appear to be important.

sis, for every stage increase of fibrosis identified (on a 1- to 4-point fibrosis scale) on initial liver biopsy, there was a 2-fold increase in future complications or death (relative risk, 2.4; 95% confidence interval [CI], 1.6–3.6).<sup>13</sup> Finally, patients with fibrosis regression may be protected from developing clinical complications.<sup>14</sup>

Although fibrosis is commonly accepted as the precursor to cirrhosis, and therefore is likely to be associated with adverse outcomes, a word of caution is essential in unequivocally assigning its importance. For example, in a cohort of patients with chronic HCV and histologic (only) cirrhosis, it appeared that only patients who developed a complication had an adverse outcome.<sup>15</sup> Perhaps the most difficult issue in this area is understanding what predicts whether a patient with fibrosis will develop a complication.

### Tools Used to Quantitate Fibrosis

The historical “gold standard” for assessment of fibrosis is histologic assessment of the liver (liver biopsy).<sup>16</sup> However, liver biopsy is invasive and is asso-

ciated with serious potential complications, requires substantial training and skill, makes both patients and physicians anxious, and can be associated with substantial sampling error. For example, in a series of 124 patients with chronic HCV infection who underwent laparoscopy-guided biopsy of the right and left lobes, 33.1% had a difference of  $\geq 1$  histologic stage (modified Scheuer system) between lobes.<sup>17</sup> Furthermore, in 51 patients with nonalcoholic steatohepatitis (NASH) undergoing sequential biopsies, 6 of 17 patients with bridging fibrosis on 1 sample had only mild or no fibrosis on the other.<sup>18</sup>

Because liver biopsy is invasive, and histologic assessment of the liver imperfect, there has been great interest in non-invasive measurement of fibrosis; many methods have been proposed (Table 1). Bedside clinical signs are generally evident only when cirrhosis and portal hypertension are present; they are of little value in assessing early stages of liver fibrosis. Routine laboratory values such as platelet count are abnormal primarily in patients with advanced disease.<sup>19</sup> In patients with HCV, an aspartate aminotransferase (AST) to alanine aminotransferase ratio  $>1$  may suggest the presence of cirrhosis.<sup>20</sup> A model using the AST and platelet count (AST to platelet ratio index [APRI]), has value in fibrosis assessment.<sup>21</sup> Serum markers, either individually or combined as panels may predict liver fibrosis.<sup>22</sup> Additionally, many radiographic tests have been examined; ultrasound, computed tomography, and magnetic resonance imaging are generally capable of detecting evidence of portal hypertension, but are typically insensitive for mild or moderate fibrosis. Finally, models including combinations of clinical signs, routine laboratory tests, radiologic imaging modalities, and/or quantitative assays of liver function may predict liver fibrosis.<sup>22</sup> An ideal noninvasive diagnostic test for hepatic fibrosis would be simple, readily available, inexpensive, and accurate. Unfortunately, at the current time, neither individual tests nor a combination of tests meets these criteria.

### Transient Elastography

Transient elastography is a novel, ultrasound-based technology that involves acquisition of pulse-echo ultrasound signals to measure liver stiffness<sup>23</sup> (Figure 2). In brief, the tip of an ultrasound transducer probe is placed between ribs over the right lobe of the liver. The probe transmits a low-amplitude (vibration and frequency) signal to the liver, which in turn induces an elastic shear wave that propagates through liver tissue. The pulse-echo ultrasound allows measurement of wave velocity, expressed in kilopascals, a measure of liver stiffness. Normal liver stiffness is reported to be in the range of 4–6 kilopascals, whereas cirrhosis is generally present at levels  $>12$ –14 kilopascals.<sup>24–26</sup>

**Table 1.** Noninvasive Methods to Assess Liver Fibrosis

| Test                   | Examples  | Advantages <sup>a</sup>   | Disadvantages  | Comments   |
|------------------------|---|---|--|--|
| Physical exam          | Spider angiomata, splenomegaly                    | Very simple and readily available, inexpensive                                    | Indirect, low sensitivity and specificity                            | Limited usefulness   |
| Simple blood tests     | Platelet count, AST                               | Very simple and readily available, inexpensive                                    | Indirect, low sensitivity and specificity                            | Limited usefulness   |
| Serum makers           | Hyaluronic acid<br>Type I collagen<br>Fibronectin | Simple, quantitative  | Indirect, low sensitivity and specificity, availability limited      | Limited usefulness   |
| Imaging                | Ultrasound<br>MRI<br>CT                           | Simple, readily available, large previous experience                              | Low sensitivity and specificity, generally costly, radiation with CT | May be helpful as a tip off to portal hypertension   |
| Marker panels          | “ELF”<br>“FPI”<br>“Fibrotest”<br>“Fibroscan”      | Enhanced sensitivity and specificity, quantitative                                | Indirect, availability limited, some are costly                      | May also be useful for tracking a change in fibrosis status  |
| Transient elastography | “Fibroscan”                                       | Results immediately available, quantitative, enhanced sensitivity and specificity | Some technical limitations, availability limited                     | Cost unclear, may also be useful for tracking a change in fibrosis status, stiffness correlates with portal hypertension |

<sup>a</sup>All tests theoretically offer a measure of global fibrosis compared to the localized sample that liver biopsy and histology provides.

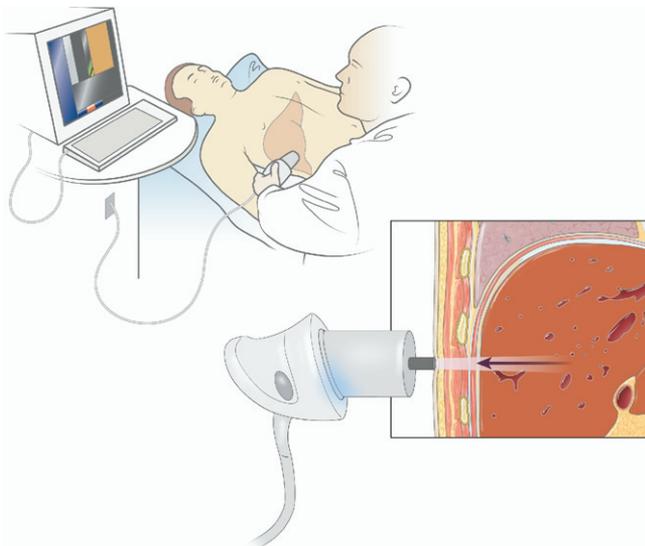
Transient elastography is associated with attractive features beyond the fact that it is noninvasive. Most important, it assesses a relatively large sample—across an area of 1–2 cm of the liver, estimated to be some 100 times greater than a liver biopsy specimen. Additionally, transient elastography allows multiple readings to be taken (from slightly different areas, thereby providing data on an even larger sample). This is critical because sampling

error associated with liver biopsy<sup>17,18</sup> is likely due to the small portion of the liver sampled.<sup>27</sup>

### Transient Elastography and Fibrosis

The pathophysiologic basis of liver “stiffness,” and the degree to which fibrosis correlates with liver stiffness, is an area of active investigation. Indeed, the relationship of fibrosis to the “mechanical” or “physical” state of the liver is not well understood, although it has long been appreciated that the cirrhotic liver is stiff. Indeed, Rene Laennec, wrote many years ago<sup>28</sup>: “The liver, reduced to a third of its ordinary size . . ., one could not mash but a small portion: the rest gave to the touch the sensation of a piece of soft leather.” Investigation over the last 2 decades has more precisely evaluated tissue elasticity, typically using ultrasound technology.<sup>29–32</sup> One study evaluated the consistency of the liver as a change in a resonance frequency.<sup>33</sup> In patients undergoing hepatic resections for various indications, liver stiffness was measured intraoperatively and correlated with both liver function and liver fibrosis.

It is further known that the injured liver itself is contractile (and thus has elastic properties), presumably as a result of cellular elements within the liver such as myofibroblasts.<sup>34</sup> Liver fibrosis appears to be characterized by elements of reversible and irreversible fibrosis; the irreversible component may be made up of relatively acellular bands of cross-linked collagen,<sup>35</sup> the latter possibly associated with reduced elasticity. Thus, a fundamental pathophysiologic question is this: Do elements at the cellular level play a role in determining tissue elasticity?



**Figure 2.** The figure depicts an overview of the technique. Briefly, a pulse-echo ultrasound signal is obtained by placing a transducer probe between ribs over the right lobe of the liver. The low amplitude signal transmitted to the liver induces an elastic shear wave that propagates through liver tissue. The pulse-echo ultrasound allows measurement of wave velocity obtained provides a measure of liver stiffness.

This is highly likely; in fact, it was suggested that liver stiffness precedes fibrosis and stellate cell activation, raising the possibility even that fibrosis and liver stiffness may not be linked.<sup>36</sup> We know that liver fibrosis is a result of activation of effector cells (stellate cells, fibroblasts, fibrocytes) with subsequent fibrogenesis. Additionally, liver stiffness may be increased in the setting of hepatic inflammation; thus, a “cellular” contribution to liver stiffness is attractive. Nonetheless, further investigation is clearly required to test this possibility.

Given this background, it is clear that there are many issues surrounding the use of transient elastography for quantitation of liver fibrosis including several highlighted below.

1. How accurate is transient elastography and can it differentiate no fibrosis from very early fibrosis stages? Will measurement of liver stiffness allow longitudinal quantitation of fibrosis as the patient transitions from F1 to F2 to F3?
2. How reproducible and reliable is it?
3. How much training is required?
4. Are differences in gender important?
5. What is the cost? Is it cost effective?
6. What are the limitations of transient elastography?
7. How might transient elastography be used in clinical practice?

### Accuracy

Transient elastography has been shown to have a reasonably high sensitivity and specificity for fibrosis at both ends of the spectrum. Transient elastography appears to be able to tell us that the liver is either normal or cirrhotic. For example, in a prospective multicenter study of 327 chronic HCV patients, the AUROC for METAVIR stage  $\geq$ F2 and cirrhosis (F4) were 0.79 and 0.97, respectively.<sup>24</sup> Many other studies have yielded similar results.<sup>25,37-44</sup> Liver stiffness measurements have been shown to correlate with fibrosis in a variety of liver diseases, including primary biliary cirrhosis,<sup>45</sup> primary sclerosing cholangitis,<sup>45</sup> NASH,<sup>46</sup> and others.<sup>39</sup>

It is likely that transient elastography can be used in combination with other (noninvasive) tests to more accurately assess fibrosis stage. In a prospective analysis comparing transient elastography, serum markers, and the APRI in a cohort of 183 chronic HCV patients with evenly matched F1–F4 disease, the performance of the various noninvasive tests was similar (the AUROC for transient elastography, serum tests, and APRI were 0.83, 0.85, and 0.78, respectively, for METAVIR F  $\geq$ 2).<sup>47</sup> However, the best overall performance was obtained by combining transient elastography and serum markers (AUROC of 0.88 for F  $\geq$  2, 0.95 for F  $\geq$  3, and 0.95 for F = 4).

Although the “global” accuracy of transient elastography is high, it is imprecise in quantitating intermediate levels of fibrosis (as is the case with serum markers). Thus, it is difficult to differentiate the normal liver from METAVIR stage F1, stage F1 from F2 disease or even stage F2 from F3 disease. To the degree that this degree of differentiation may be important from a clinical management standpoint, the use of transient elastography will be limited.

### Reproducibility and Reliability

Transient elastography is reported to have good reproducibility with low variability. Intraobserver and interobserver agreement were analyzed using the intraclass correlation coefficient (ICC) and correlated with different patient-related and liver disease-related covariates, in one study.<sup>26</sup> In 800 examinations (in 200 patients), the overall interobserver agreement ICC was 0.98 (95% CI, 0.977–0.987). Increased body mass index (BMI,  $.25 \text{ kg/m}^2$ ), steatosis, and low staging grades (<F2) were significantly associated with reduced ICC ( $P < .05$ ).

### Training

Certain clinical features may be associated with acceptable performance and success of transient elastography.<sup>48</sup> The success rate of “shots” (ie, a valid measurement) decreased with age, and was lower in obese than in those with lower BMIs.<sup>48</sup> Operators who had performed  $\geq$ 50 prior examinations had a higher success rate. Additionally, reproducibility was significantly reduced in patients with steatosis, increased BMI, and lower degrees of hepatic fibrosis. In another study,<sup>40</sup> the only factor associated with technical failure of the study was BMI  $>$  28.

### Gender

There may be differences in liver stiffness among men and women. In a cohort of normal individuals, the median liver stiffness value was 4.8 kPa (range, 2.5–6.9) and did not correlate with age, body weight, or height, but it was significantly higher in men than in women ( $5.2 \pm 0.7$  vs  $4.5 \pm 1.0$ ;  $P < .01$ ); other variables did not differ among the genders.<sup>49</sup> These data suggest an intrinsic difference in fibrogenesis in men and women. Experimental data support the possibility that female hormones protect against fibrosis.<sup>50</sup> Larger studies of normal individuals are required to more robustly assess this issue.

### Limitations

In addition to the issues related to accuracy and extension of its use in populations other than those with known liver disease, several important technical limitations merit comment. First, to obtain a high-quality pulsed signal, there must be a direct and relatively short path to the liver. The depth of signal penetration is limited, so it is difficult to perform transient elastogra-

phy in obese patients or those with ascites. In addition, ribs may obscure the pulsed signal. It is likely that newer transducers will overcome at least some of these issues.

An important limitation to date is that transient elastography has been performed largely in patients with known liver disease. Because the experience with general populations is limited, it is unknown whether transient elastography will be useful as a widely applicable screening tool. For example, because liver fibrosis likely varies with age,<sup>51</sup> better standards among normals are required.

An inherent limitation of the published literature is that liver histology obtained by biopsy has been used as a “gold standard,” and itself, although considered the best measure of fibrosis, is associated with sampling error,<sup>17,27</sup> not surprising given that liver biopsy samples a small fraction of the liver. Therefore, because liver biopsy itself may not be truly reliable, it is difficult to accurately assess tests compared to it.

### **Use in Practice**

Perhaps the greatest clinical utility of transient elastography will be its ability to determine whether the patient has cirrhosis. The specificity of transient elastography in patients with known liver disease has been reproducibly in the 90%–95% range.<sup>44</sup> Thus, a measurement in the 8–9 kilopascal range would suggest less severe fibrosis, perhaps at a METAVIR F2 level, and unlikely histologic cirrhosis (ie, a false positive for cirrhosis). Thus, transient elastography appears to be best at excluding cirrhosis (with a liver stiffness threshold of  $\approx 14$  kilopascals). False negatives appear to be attributable largely to inactive or macronodular cirrhosis.<sup>42</sup> If the clinician believes it is important to know the precise (particularly, intermediate) stage of fibrosis, then transient elastography is unlikely to be definitive.

An attractive area for transient elastography is that it may assist clinicians in ascertaining the severity of liver disease at the bedside. In one study,<sup>38</sup> physicians were asked to predict the stage of fibrosis using clinical data alone and then again after addition of transient elastography data. Interestingly, the clinician’s ability to predict cirrhosis was significantly improved, although improvement in prediction of other stages was less pronounced.

### **Transient Elastography and Portal Hypertension/Varices**

Although the pathophysiologic basis for use of transient elastography as a surrogate for fibrosis seems relatively straightforward, the basis for its correlation with portal hypertension remains poorly defined. In virtually all forms of intrahepatic liver disease, portal hypertension initially develops as the result of an increase in intrahepatic resistance. However, as portal hypertension advances, increased portal pressure appears to be perpet-

uated largely by (increased) flow derangement in the splanchnic circulation.<sup>52</sup> Thus, it might be predicted that transient elastography could predict changes in intrahepatic vascular resistance resulting from effector cell activation at the level of the sinusoid (ie, early in the disease process). Notwithstanding, it would be predicted that transient elastography should not be able to measure complex hemodynamic (especially flow) abnormalities typical of advanced portal hypertension.

Liver stiffness appears to correlate with HVPG measurements. In a study of 61 consecutive patients with HCV,<sup>53</sup> the correlation was excellent in patients with HVPG < 10, but was less optimal for HVPG values > 10 mm Hg. The AUROC for prediction of HVPG > 10 and > 12 mm Hg were 0.99 and 0.92, respectively, and at liver stiffness cutoff values of 13.6 kPa and 17.6 kPa, sensitivity was 97% and 94%, respectively. There was also good correlation between liver stiffness and the presence of esophageal varices but not between liver stiffness and variceal size. Other studies have demonstrated a correlation between increasing liver stiffness and variceal size.<sup>54</sup> Because the degree of fibrosis appears to correlate with portal hypertension,<sup>12</sup> the fact that liver stiffness measured by transient elastography also correlates with portal hypertension suggests that fibrosis and portal hypertension are linked, either directly or indirectly.

### **Summary and the Future**

Transient elastography appears to be capable of providing reliable and reproducible quantitative measurements of liver stiffness, which in turn can be correlated with fibrosis. This provides further evidence that the practice of hepatology may shift toward use of noninvasive tools to assess disease. Perhaps one of the greatest potential uses for measurement of liver stiffness with transient elastography is in prediction of portal hypertension (and esophageal varices). This is likely because transient elastography appears to accurately measure advanced fibrosis, which appears to correlate with portal hypertension. Unfortunately, transient elastography does not appear to be robust at discriminating between intermediate grades of fibrosis, and is really not helpful in assessing early fibrosis. To the extent that these data may be important in clinical management, transient elastography alone will be limited in clinical practice.

Notwithstanding the enthusiasm for transient elastography, many questions remain. Could MR elastography provide a better global assessment of the liver? Can transient elastography be used as a screening tool in patients without known liver disease (ie, to screen obese patients for the presence of nonalcoholic fatty liver disease or NASH)? What will it cost and will it be cost effective compared with other noninvasive tests or

liver biopsy? Most important, it will be essential for us to learn whether transient elastography can be combined with other clinical data or other noninvasive tests to provide a more accurate measure of fibrosis. As with all diagnostic tests that strive to assess liver fibrosis, we need more natural history data, we must understand how well the diagnostic test informs us about long-term outcomes. In summary, the field is moving forward, and noninvasive assessment of liver fibrosis will likely soon be realized.

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