Ultrasound-based Hepatic Elastography
Origins, Limitations, and Applications

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Abstract: A reliable, noninvasive marker to help clinicians evaluate hepatic fibrosis is urgently needed. The liver biopsy, an imperfect gold standard, has recognized limitations including sampling error and interobserver variability. Hepatic elastography (HE) is a novel sonographic method for assessing liver stiffness and has excellent accuracy in making the diagnosis of minimal fibrosis and cirrhosis. Several conditions intrinsic to the pathology of the liver compromise the positive predictive value of HE for fibrosis alone including acute hepatitis, obstructive cholestasis, and passive congestion. Technical considerations that hinder the performance of elastography include an advanced body mass index, the presence of ascites and narrow intercostal spaces. Despite these limitations, elastography has a role in staging fibrosis, prognosis of disease outcome, surveillance, and treatment decisions. HE is now being used in lieu of liver biopsy to investigate the natural history of chronic liver diseases. Additional studies are required to better define the appropriate role of HE in clinical practice.

Key Words: hepatic elastography, transient elastography, Fibroscan, noninvasive markers of fibrosis, cirrhosis

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Liver fibrogenesis is the wound-healing response and "final" pathway of chronic liver disease.[1] Accurate staging of fibrosis is valuable for prognosis, treatment decisions, and surveillance of disease progression or regression.[2,3] Liver biopsy, currently the gold standard[4] has several recognized limitations including sampling error and interobserver variability in interpretation and staging.[5] Furthermore, the dynamic process of fibrosis resulting from progression and regression is difficult to capture with biopsy alone.[6] The hepatology community is actively researching noninvasive methods of fibrosis quantification.

Hepatic elastography (HE), which uses the novel method of transient elastography (TE), has been extensively evaluated in many different forms of liver disease as a tool to measure liver stiffness as a surrogate for fibrosis. However, as it is not widely available in the United States and is awaiting FDA approval, there is considerable uncertainty about elastometry's niche within the day-to-day practice of hepatology.[7] Perhaps the most critical question for clinicians, as multiple methods develop for the evaluation of fibrosis, is how to cost effectively and safely incorporate this multimodality approach into clinical care. The aim of this review is 3-fold: (1) to provide background that sets the stage for the emergence of HE as a leading noninvasive marker candidate, (2) to identify the strengths and weaknesses of HE, and (3) to describe how it is being applied to the clinical and research setting.

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A NEED FOR NONINVASIVENESS

Our understanding of liver fibrogenesis has led to new insights that liver fibrosis is not a relentless and progressive condition. Gone is the dogma of fibrosis following a single, common pathway. New insights dictate that clinically significant histologic improvement can occur even in a cirrhotic liver.[8] Pathways favoring fibrogenesis include stellate cell activation, the process of epithelial-to-mesenchymal transition (EMT) of hepatocytes and cholangiocytes, activation of resident portal fibroblasts and bone marrow-derived fibrocytes.[9] There is additional variability within pathways, with the composition of extracellular matrix (ECM) changing over time. At the earliest stages of fibrogenesis, elements such as collagen-type IV, heparin-sulfate proteoglycans, and laminin predominate, whereas the ECM of more established fibrosis is dominated by fibril forming collagens type I and III.[9] There is, however, a definite inability to accurately measure fibrogenesis and fibrosis regression in vivo using any of our currently available technologies. To really look at these dynamic changes, we will probably need to advance molecular imaging of the cells involved in liver fibrosis and regression.

Thus it is essential to have an accurate method to quantify the amount of fibrosis regardless of stage, underlying pathway or disease etiology. To this end liver biopsy has been the clinician and investigator's gold standard for decades. Beyond its diagnostic capability, liver biopsy is an invaluable tool for clinical prognostication as it relates to the stage of fibrosis. For a clinician, defining the stage of liver fibrosis provides a general estimation of disease chronicity and severity. Clinically relevant outcomes in liver disease are often a result of advanced fibrosis or cirrhosis, with eventual development of portal hypertension and hepatocellular carcinoma. In fact, septal thickness and small nodularity are 2 histologic features independently predictive of clinically significant portal hypertension (HVPG $\geq$10).[10] In addition, HCC occurs primarily in the setting of cirrhosis and one can argue that the major role of biopsy is in diagnosing or excluding advanced fibrosis and cirrhosis so that appropriate screening can be undertaken.

In addition, the fibrosis stage has been used to determine the relative urgency for disease treatment, especially with highly prevalent, indolent conditions such as hepatitis C virus infection and nonalcoholic steatohepatitis. Valid recognition of the extreme ends of the fibrosis

spectrum, therefore, would either allow for a cautious, cost-effective delay of treatment or herald imminent treatment and surveillance for the complications of cirrhosis. This paradigm helps define the utility we seek in noninvasive biomarkers. In effect, categorizing an established diagnosis as early or late in its natural history can add efficiency to treatment algorithms and provide important prognostic information for both the patient and clinician.

However, the need for staging disease is also dependant on the outcome of treatment; as treatment becomes more effective the need for staging disease precisely becomes less necessary and the need to exclude cirrhosis more important. For example, in genotype 2 and 3 HCV, biopsy is not necessary as over 80% of patients achieve a sustained virologic response that is independent of disease stage. In such cases, biopsy can be reserved for those that fail to respond.

A biopsy is said to represent 1/50,000 of the liver,[11,12] and therefore it is not surprising that sampling error frequently occurs. The actual frequency is an area of debate; 25% to 30% is commonly ascribed, with understaging occurring especially at the lower strata of fibrosis.[13,14] In a recent paper by Robert et al,[15] the percentage of disagreement between hepatopathologist and community pathologist assessments for staging hepatitis C ranged between 22 and 58% depending on the stage of fibrosis, and was augmented in biopsy samples less than 1.5 cm. In addition to the propensity for sample error and inter-observer interpretation, liver biopsy suffers from poor patient acceptance because it is invasive and sometimes painful.[16] Furthermore, there is a small but significant risk for serious complications and death,[4] even when carried out transjugularly. Toward the future, as more clinical trials of antifibrotics are designed, serial biopsy will unlikely be the sole evaluator of regression, and therefore, noninvasive methods are paramount.

Mehta et al evaluated a critical aspect in the search for the ideal noninvasive marker of fibrosis.[17] Assuming a conservative error rate for biopsy staging of 10% to 20%, how is it possible to validate a perfect alternative when it is compared with an imperfect standard? Their model suggested that the area under the ROC curve for a surrogate marker for fibrosis compared with liver biopsy could not exceed 0.9. In effect, biopsy error causes the true validity of surrogate tests to be underestimated. This will in turn lead a clinician to falsely misperceive the test as inaccurate, when in fact it is possible that a perfect surrogate marker could already exist.

The ideal noninvasive marker should have certain characteristics for practical application. For an imaging modality such as elastometry, salient features should include: ability to accurately determine fibrosis stage; reliability unaffected by the underlying disease and conditions intrinsic to hepatopathology; ease of performance and reproducibility. These characteristics are similar to ones earlier described for serologic markers of fibrosis.[18] Studies thus far suggest that HE possesses many of the characteristics of an ideal marker, and will be elaborated in this review.

ELASTOGRAPHY AND FIBROSIS STAGING

The evolution of elastography in the field of hepatology took many forms over nearly 2 decades before finding success in HE.[19] The methods of static, dynamic and remote elastography were all first attempted without success. The primary reason was the boundary effect, or motion artifact from respiration that interferes with hepatic imaging. Those methods proved more successful with breast[19,20] and prostate[19] evaluation.

A sentinel study by Yeh et al[21] from China, published in Ultrasound and Medical Biology in 2002, laid the foundation for HE when it was shown that liver stiffness positively correlated with fibrosis. Partial hepatectomy specimens were sectioned into blocks and placed on an electronic balance. This balance was connected to a personal computer and acrylic compressor, which was lowered on to the tissue. The compressor then applied intervals of increasing pressure (in kPa), allowing for measurement of the internal displacement of liver tissue. In effect, healthier livers allowed for greater internal displacement whereas cirrhotic livers, stiffer by nature, had less internal displacement. Interestingly, this correlation was greatest at the ends of the fibrosis spectrum, and suffered from poor discriminatory ability at the middle strata of fibrosis. This dilemma would prove to haunt HE's applicability throughout subsequent clinical investigations.

This technology was initially used in the cheese industry as a way to evaluate the internal stiffness of large blocks of cheese. Echosens (Paris, France) capitalized on the shear elasticity of another soft solid material and developed the now widely used FibroScan unit. The hand-held probe is placed in the intercostal space overlying the right, lateral lobe of the liver. It sends out 2 types of waves. The first, a shear, mechanical wave, propagates through firm tissue quickly, and through healthy tissue more slowly. The second type of wave emitted by the probe is an ultrasound wave. At a depth between 2.5 and 5.5 cm from the skin, successive ultrasound waves reach a propagating shear wave at a given distance apart, depending on the velocity of that initial shear wave (Fig. 1). The distance between the 2 points can then be used to calculate the shear wave velocity, and in turn, through a mathematical model using Young modulus, the stiffness is determined.[19] The

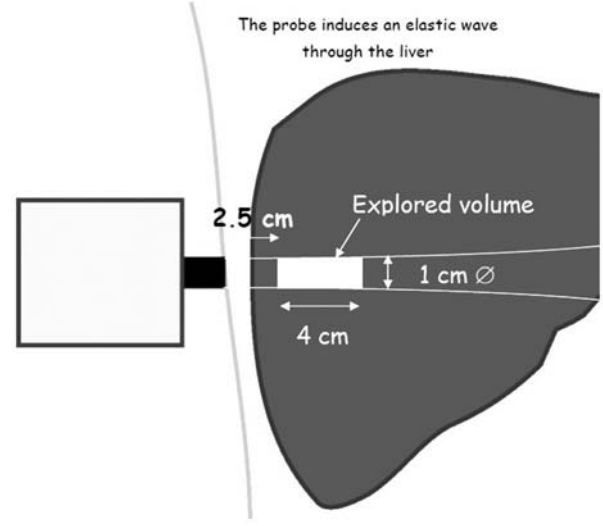

FIGURE 1. The probe is placed between ribs overlying the liver. It emits 2 types of waves (mechanical, ultrasound) and gathers information from a field that is roughly 100 times larger than that explored by a liver biopsy.

area of liver surveilled by FibroScan is 100 times that of liver biopsy, and can be expanded by sampling in different intercostal spaces.

The original manuscript published by Sandrin et al in 2003 evaluated a cohort of chronic hepatitis C patients, all with abnormal aminotransferase levels. Importantly, liver stiffness correlated well at both F0 and F4 stages of fibrosis. Perhaps not surprisingly, there was poor discriminatory ability between metavir F1 and F2 stages of fibrosis (Fig. 2). These observations mirror the diagnostic ability of other, noninvasive markers of fibrosis, namely serologic panels. It is unclear what accounts for the overlap within intermediate stages, although it suggests that our current staging system is an oversimplified representation of a more fluid spectrum of disease. In general, transient elastography is as good as the serologic markers (Fibrotest, Lok Index, APRI, Prothrombin index, AST/ALT ratio, and platelet count) to diagnose the earlier stages of fibrosis (31). Elastography has superior accuracy in the detection of cirrhosis, with an AUROC of 0.96, versus the serologic markers (AUROC from 0.61 to 0.82) (31). A separate study found that combining HE with a serologic marker of fibrosis, such as APRI, significantly enhanced the prediction of fibrosis stage. However, combinations of 3 or 4 tests led to redundancy and increased cost.[22]

With respect to liver biopsy, HE correlates very well with established cirrhosis. Although considered the gold standard, biopsy is susceptible to understaging, and there is the potential for a correlative discrepancy when elastography is suggestive of cirrhosis. The quality of the biopsy is therefore important, and fortunately, most studies incorporate the quality of the tissue sample.

Transient elastography and biopsy were compared in a group of 100 patients coinfected with HCV and HIV, and diagnostic values were compared by calculating the area under the ROC.[23] Liver stiffness was 0.80 (0.72 to 0.89) when discriminating between F </= 1 and F > 2, 0.93 (0.85 to 1.00) when discriminating between F </= 2 and F > 3 and 0.99 (0.97 to 1.00) when discriminating between

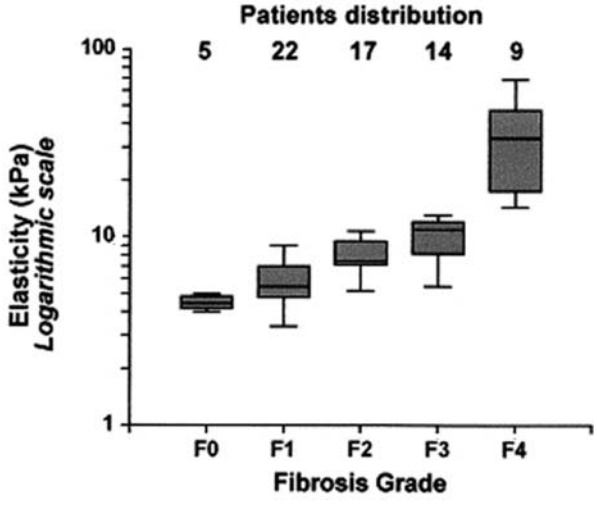

FIGURE 2. The ability to diagnose no fibrosis (F0) and cirrhosis (F4) is excellent. There is poor discriminatory ability in the intermediate strata of fibrosis (F1-3). Results from original manuscript by Sandrin et al. *Ultrasound in Medicine and Biology.* 2003;29:1705–1713.

F </= 3 and F4. The cut-off values to denote F </= 1 was 7 kPa, F >/= 3 was 11 kPa and F4 was 14 kPa.

An analysis of discordance between transient elastography and biopsy was conducted and an association with liver disease related factors was determined.[24] Thirty-four percent of 300 patients had discordant findings, the majority of which had histologic stage >/= 2 and TE < 7.1 kPa (false negative). A smaller group had stage < 2 and TE > 7.1 kPa (false positive). Importantly, no patient with discordant results had cirrhosis.

As noted above, the intermediate stages of fibrosis do not correlate well with histology. This may be in part owing to the heterogeneous patterns of fibrosis, that is, periportal, pericellular, and perivenular. It is well recognized that conditions such as hepatitis C and nonalcoholic steatohepatitis lead to different patterns, periportal and pericellular, respectively. A published morphometric analysis revealed a higher correlation between liver stiffness measurement and pericellular fibrosis ($r = 0.43$) than periportal ($r = 0.21$) or perivenular fibrosis ($r = 0.25$).[25] The variable nature of fibrosis patterns are more likely to play a role in these intermediate stages of fibrosis, compared with established cirrhosis, in which the architectural distortion is homogenous and the underlying etiology more difficult to discern.

A meta-analysis of 9 studies concurred that the ability to differentiate mild from advanced fibrosis was poor, and was partially explained by a lack of uniformity of stiffness cut-offs between the studies.[26] The stiffness cut-off level for cirrhosis from 1 study to the next contains greater variability (from 11 kPa to 19 kPa) than cut-off values diagnosing no or minimal fibrosis, (kPa < 7). A recent meta-analysis shows that significant fibrosis, stage F2 or higher, begins around 7.2 kPa.[27] Thus interpreting stiffness values at opposite ends of the fibrosis spectrum allows some flexibility without compromising discriminatory ability. The underlying liver disease etiology (viral vs. mixed) and biopsy sample size does not influence the ability to distinguish minimal from advanced disease (22). In contrast, cut-off values for intermediate stages of fibrosis are poorly established. There are too few studies to determine the influence of the specific variables such as disease etiology. Subgroup analyses could not be done reliably (22). Therefore, it can be safely concluded that intermediate stiffness values, between 6 kPa and 9 kPa, do not allow for accurate interpretation of fibrosis stage.

The cut-off values are influenced by disease states and not only the underlying disease itself. In several studies, an "active" disease state is more likely to be reflected by increased stiffness values, and this distinction is critical to accurately interpret stiffness values. The most common active disease state in the study of elastography is inflammation, common to disorders such as viral hepatitis and fatty liver disease. The category of acute viral hepatitis and steatohepatitis will be discussed in separate sections. However, in the case of a chronic active disease such as hepatitis C infection, should an elevated alanine aminotransferase level affect cut-off values? Probably not, however, shifting the cut-off threshold based on an elevated ALT value alone has been attempted. In a prospective study of a hepatitis C cohort, Wong et al[25] find that patients with similar fibrosis staging by histology but with higher ALT levels tended to have higher liver stiffness measurements. To account for this observation, the investigators increased the diagnostic threshold for stage 0 to 1 disease (6 kPa if ALT is less than the upper limit

of normal; 9 kPa if ALT is 1 to 5 times the upper limit of normal) and stage 3 to 4 disease (7.5 kPa if ALT is less than the upper limit of normal; 12 kPa if ALT is 1 to 5 times the upper limit of normal). A second study also suggests that minor ALT elevations can alter TE readings and cause discordance with histologic stage.[28] These observations reinforce the excellent predictive value of stiffness measurements at the extreme ends of the fibrosis spectrum. It also suggests that the continuous spectrum of fibrosis may be independent of ALT values and therefore ranges of stiffness levels may be preferable to absolute cutoffs.

Nearly every study conducted since has corroborated HE's excellent predictive values for the diagnosis of cirrhosis when alternative underlying variables are accounted for[29–31] (Fig. 3). The question was bound to arise…could HE be even *better* than liver biopsy at making the diagnosis of cirrhosis? In a validation study by Nahon et al[32] on a cohort of alcoholic liver disease patients, 4 patient's biopsies staged as F3 showed corresponding HE values near 75 kPa, otherwise suggestive of F4 cirrhosis. The investigators suggested that HE did not suffer from poor positive predictive value, rather, the biopsy may have been understaged and these 4 participants might have been cirrhotic. Although no conclusive evidence was offered, this point of contention is noteworthy.

An important meta-analysis by Friedrich-Rust et al[33] reaffirmed the conclusion that HE is excellent at making the diagnosis of cirrhosis. The important aspect of this study of more than 50 publications, some only in abstract form, was its inclusion of hepatitis C cohorts, nonhepatitis C cohorts,

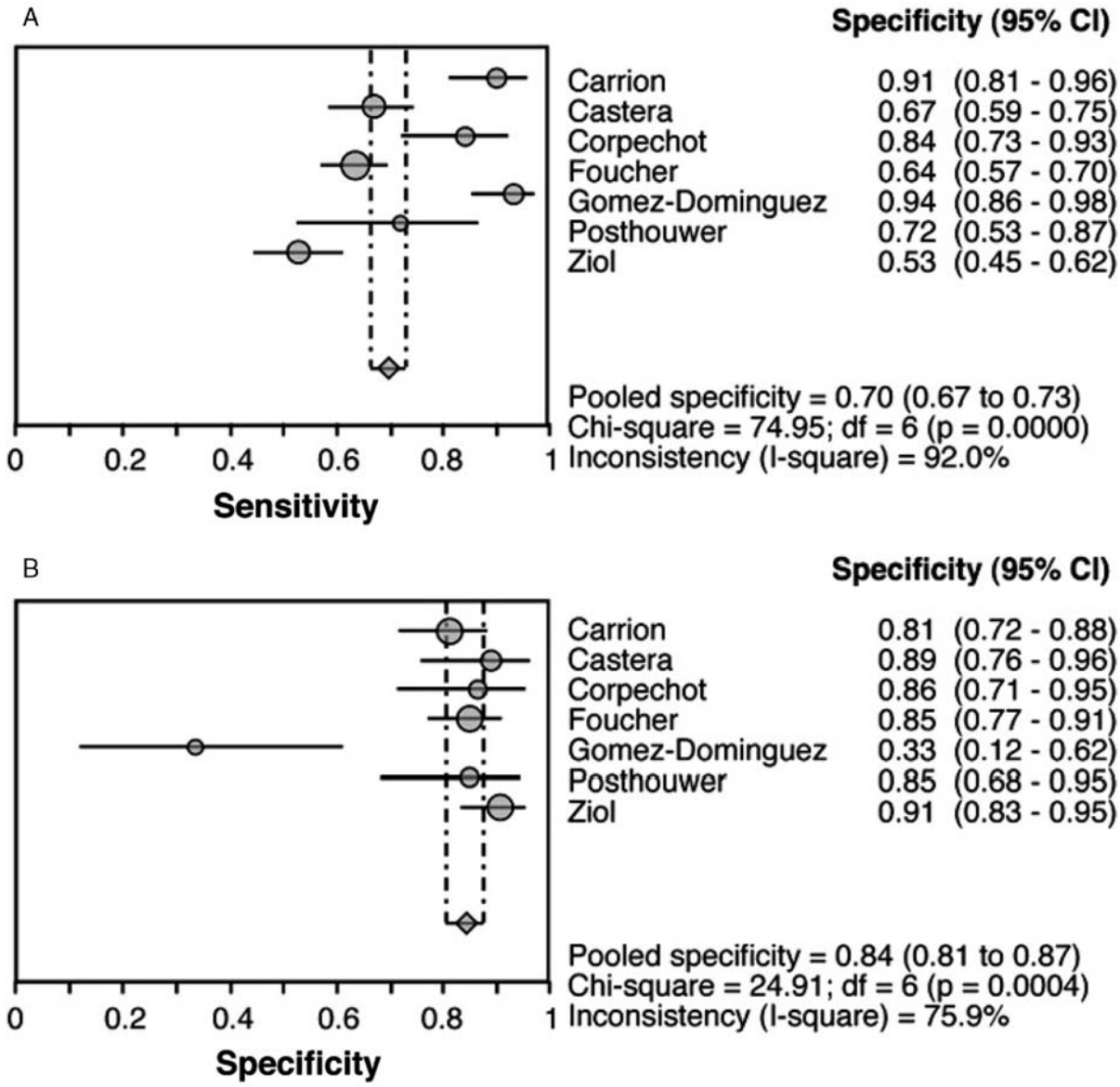

FIGURE 3. Forrest plots and meta-analyses of studies evaluating the (A) sensitivity and (B) specificity of ultrasound-based transient elastography compared with liver biopsy for the detection of stage IV hepatic fibrosis in patients with chronic liver disease. Adapted with permission from *Clin Gastro and Hepatology.* 2007.

and mixed-diagnosis cohorts. What these investigators found was that the underlying cause of liver disease had no effect on the ability to diagnose cirrhosis (mean AUROC 0.94), and even severe fibrosis, defined as F >/ = 3 (mean AUROC 0.89). However, there was considerable variability in accurately diagnosing significant fibrosis (F >/= 2) especially in studies with smaller sample sizes. It looked as if the underlying cause of liver disease played a role in stiffness values.

CONFOUNDERS OF STIFFNESS MEASUREMENT

On account of increased stiffness caused by more than just fibrosis, it is clear that pathologic conditions intrinsic to hepatopathology must also be taken into account. Fortunately, much but not all of the groundwork for understanding these potential confounders has been conducted and reported. These include studies on steatosis,[32,34,35] hepatitis,[36–42] cholestasis,[43] infiltrative disorders,[44–46] passive congestion[47] and more. Recognizing the confounding effect of these conditions is critical to the clinician's interpretation of elastometric results.

Steatosis

Yoneda et al[35] appraised the effect of bland steatosis on HE accuracy. It was evident from their results that bland steatosis does not have a confounding effect, regardless of severity. This was also concluded in several other studies,[19,29] including one that assessed healthy individuals for the presence of bland steatosis.[34] However, when the necroinflammatory component was taken into account, as in the case of NASH, hepatic stiffness increased concomitantly.[34] This suggests that NASH, but not NAFLD must be considered carefully when interpreting results. Despite the above conclusions, the literature is not unanimous in its dismissal of simple steatosis. [27,48,49]

Hepatitis

The effects of hepatitis per se on HE accuracy have been reported, and there is an emerging consensus on how to interpret elevated aminotransferase levels. Magnitude of elevation and acuity of illness are important variables.[37,42,50–53] On one extreme of the hepatitis spectrum, flares of acute or chronic disease, the conclusion is foregone: stiffness is increased.[52,53] Sagir et al published a report in 2007 on a cohort of participants with chronic hepatitis B who experienced an acute flare of their disease. Alanine aminotransferase levels ranged from as little as 151 to over 5000 IU/L. These initial values corresponded with HE measurements from 14 to 52 kPa, all within the range of advanced fibrosis or cirrhosis.

Other studies confirmed that stiffness values during a flare are higher than states of chronic viral hepatitis or the inactive carrier.[54] These cases were followed longitudinally until resolution of the flare, marked by a return to normal ALT levels, and the liver stiffness levels also decreased to single digit values. Histologic comparisons were not the intention of this descriptive phenomenon. Interestingly, there was a 2-week lag time between the resolution of laboratory parameters (ALT and bilirubin) and stiffness. This finding was not corroborated in a separate study,[53] but nevertheless serves as a red flag for cautious interpretation of HE results after flares in disease activity.

Acute flares of hepatitis are one thing, elevated levels from chronic disease[55] or even coinfection[36] could be another. Castera et al[56] report that inflammatory activity does not influence HE values in hepatitis C-infected patients and regression analysis data overwhelmingly supports the claim that ALT levels in chronic disease have no correlation to stiffness.

We have reason to believe that in the cellular milieu of the hepatic lobule during injury, there are additional factors unaccounted for that alter the viscoelastic property. In a revealing study by Georges et al,[57] where it was earlier shown that the activation of stellate cells and portal fibroblasts results from increasing substrate stiffness, the same hypothesis was tested in an in vivo rat model of injury with carbon tetrachloride. The investigators found that not only did liver stiffness increase progressively with ongoing liver injury, but that the development of fibrosis *lagged behind* the development of stiffness. Although it is still unclear what causes this prefibrosis change in stiffness, it is likely that the extracellular matrix undergoes significant dynamic changes with acute injury that is irrespective of the amount of fibrosis. This property is probably one reason for any discrepancy of opinion on the topic of hepatitis and HE accuracy.

Sinusoidal Congestion

Yet another factor intrinsic to hepatopathology is sinusoidal congestion. Passive congestive hepatopathy was highlighted as a case report in a patient with chronic hepatitis C and mildly elevated serum aminotransferase levels.[47] Before the cardiac transplant and ostensibly as an evaluation of hepatic reserve, the patient was biopsied after HE revealed a level of 44.3 kPa, highly suggestive of cirrhosis. Histology showed dilated sinusoids and perisinusoidal fibrosis, but periportal fibrosis was limited. Eighteen months after cardiac transplantation, with ALT still mildly elevated, repeat HE revealed a level of just 3.8 kPa, and a repeat liver biopsy confirmed early fibrosis. LeBray et al concluded that congestive hepatopathy lowers the positive predictive value of HE. This study also initiated dialogue about additional factors related to a plethoric liver, such as the use of nonselective β-blockade, postprandial portal hyperemia, and what effect these have on stiffness.

Extrahepatic Cholestasis

Extrahepatic cholestasis is another variable that has been studied.[43] In a series of 15 cases of extrahepatic obstruction, serial HE measurements were used in addition to serum markers of cholestasis. In all but 1 case, biliary stenting was carried out for various causes of obstructive jaundice. Preintervention and postintervention bilirubin levels documented successful resolution of the obstruction. Interestingly, in all but 2 cases, the liver stiffness also decreased postintervention. Of note, several more cases showed only a trivial decrease in stiffness values, but the general trend was such that a firm conclusion was possible. Acute biliary obstruction also accounts for falsely elevated measurements of stiffness.

Extrinsic Factors

There are also conditions extrinsic to the liver that may confound, or, in some cases, altogether preclude the gathering of reliable HE data. The presence of ascites, even in small amounts, negates the applicability of elastography. This, fortunately, is a situation that begs the question. These patients will be cirrhotic by virtue of the presence of their ascites. Advanced age has been reported to affect performance and success of data acquisition.[58] Narrow

intercostal spaces are another recognized element extrinsic to the liver that makes data acquisition difficult.[59] A second-generation probe, engineered for such cases, is in development.

Obesity is also a major hindrance to the practical application of elastography. It is another variable that has attracted much international debate and has yet to be fully resolved. To obtain reliable measurements, the operator must gather a total of 10 elastographic values; successful acquisition must occur 60% of the attempts and the interquartile range of all successful measurements should be less than 30% of the median value.[39,49] As mentioned earlier, the probe begins measurement just 2.5 cm from its tip, and therefore, a habitus replete with central adiposity becomes problematic. Again, second-generation probes said to overcome the limits of advanced body mass index (BMI) are in development.

The French group led by Castera found that with BMI $> 30\,kg/m^2$, there is a failed rate (zero successful acquisitions) in 3% of cases, and unreliable results (< 60% successful acquisitions or IQR > 30%) in 15.8% of cases.[60] In other manuscripts, BMI cutoffs of 28[61,62] and 30[63] are also reported. This last example quoted a failed acquisition rate of 25% when BMI is $> 30\,kg/m^2$. In sum, the exact cutoff is not established. This may be owed to the fact that BMI does not always correlate with thoracic adiposity/wall thickness. It also remains to be determined whether unsuccessful acquisition of HE data in itself, owing to overweight, can be used for any predictive value. As several serologic panels of fibrosis markers have been previously validated[64] and possess acceptable diagnostic accuracy, their combination with failed HE from obesity could also prove useful.

TOWARD THE NATURAL HISTORY OF DISEASE

Although most research efforts thus far attempted to validate HE against liver biopsy, perhaps an equally apropos translation is to validate HE against the hepatic venous portal pressure gradient, or HVPG. After all, most clinical outcomes in end-stage liver disease are tightly correlated with advanced portal pressures, including detection of esophageal varices, first variceal bleed[65,66] and development of hepatocellular carcinoma.[67] Several studies validated HE as a noninvasive means of diagnosing portal hypertension.[38,68,69]

The report by Vizzutti et al[70] offers an excellent figure depicting this relationship (Fig. 4). Elastography can indeed diagnose earlier stages of portal hypertension, as the major determinant at gradients between 5 and 12 mm Hg is intrahepatic fibrosis. Beyond this 10 to 12-mm Hg threshold, when the sequelae of elevated portal pressures occur with greater frequency, elastography loses its correlative ability and its well-fitted regression line. The investigator's explanation focuses on the physiologic factors extrinsic to the liver that impact HVPG at these advanced gradients. These factors include portosystemic collateral development, splanchnic vasodilatation, and hyperdynamic circulation. The performance of liver stiffness for predicting significant portal hypertension, defined by HVPG >/= 10 mm Hg was found to be 92% predictive with a cutoff of 21 kPa.[71] This finding was compared with the accuracy of the prothrombin index, a previously validated serologic marker, and found to be superior. Although the data supporting the ability of HE to diagnose portal hypertension is strong,[71,72]

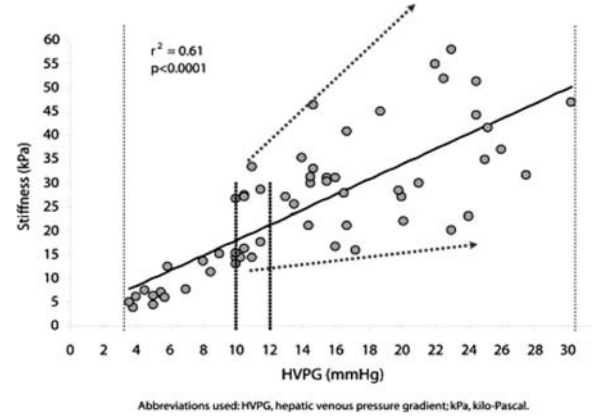

FIGURE 4. Elastometry is predictive of portal hypertension although it lacks accuracy above a pressure gradient above 10 mm Hg. This is thought to be owing to physiologic factors extrinsic to the liver in advanced cirrhosis, including the hyperdynamic circulation, the presence of portosystemic collaterals and splanchnic vasodilatation. Adapted with permission from *Gastroenterol Clin Biol.* 2008;32:80–87.

the overall data supporting its role in evaluating the consequences of portal hypertension remain unconvincing.[73]

There has been an inevitable, fundamental shift in the focus of HE studies over the past year toward an investigation into the natural history of disease. This comes as the validation studies and limitation studies reinforce similar conclusions with respect to overall efficacy of HE. These studies by and large aim to exploit elastography's ability to diagnose advanced fibrosis or cirrhosis. One such study looked at hepatitis B virus DNA and ALT levels in HbeAg negative patients to predict cirrhosis.[74] The percentage of patients with probable or possible cirrhosis increased with increasing ALT levels, and these findings were subdivided into gender and showed the relative increased risk for males to have HE cirrhosis. Furthermore, DNA evaluation showed a positive correlation with possible and probable cirrhosis, with higher rates corresponding to DNA levels greater than log 6. Other studies predicting advanced fibrosis in cohorts with HCV/HIV coinfection and metabolic syndrome have also been conducted[75] with HE as a primary diagnostic tool.

As it is now recognized that significant regression of fibrosis can occur, even in cirrhotic livers, there is great interest in clinical pharmacologic trials for antifibrotics, with no lack of candidates. Of the myriad categories there are inhibitors blocking the activation, migration or proliferation of hepatic stellate cells, hepatocyte maintenance and protection, plant-derived drugs, and even commoner agents such as statins and interferons. One of the first trials using HE to evaluate regression of stiffness as a marker of fibrosis was published in 2008 by Vergniol et al.[76] These investigators used standard treatment of Peginterferon and Ribavirin in cases of hepatitis C and measured stiffness before and after treatment. Although the no therapy arm showed no change in stiffness values, each of the 3 study arms showed an effect: nonresponders (10.3% decrease in stiffness), responders/relapsers (29.5% decrease) and sustained virologic responders (24.5% decrease). Although there is no evidence of actual regression of fibrosis, and decreased inflammation can be

responsible for decreased stiffness, this study nevertheless proved that HE can be successfully employed to monitor regression of fibrosis in such trials.

The liver transplant community also eagerly awaits additional trials using HE. To date, only hepatitis C recurrence has been adequately studied.[69,77–79] These trials used protocol liver biopsies anywhere from 1 to 2 years posttransplant and showed accuracy for staging of fibrosis, similar to the hepatitis C in a native liver. Acute viral recurrence immediately after transplant and acute cellular rejection has not been adequately studied, and it remains to be seen whether HE can help differentiate one diagnosis from the other in cases of elevated liver tests at early time points in the liver allograft. In essence this would exploit the other factors that are readily measured by elastography, such as flares of hepatitis and prefibrosis changes in stiffness. Utilization of HE in clinical practice for indications other than fibrosis staging has been suggested.[80]

With all that has been learned from the studies of HE and the liver since the first publication in 2003, it is now important to ask how this technique can impact day-to-day practice in 2010 and beyond. It seems logical that HE could be used to stage fibrosis from chronic hepatitis C infection. With this diagnostic challenge in mind, some investigators argue that many, if not a majority, of liver biopsies can be avoided altogether. This could amount to a substantial decrease in the overall number of liver biopsies, considering that 50% to 60% of all biopsies are ostensibly for staging purposes.

For example, if HE gives a low value, below 6 kPa, no biopsy is required and serial HE measurements are warranted. This approach seems reasonable. Of participants with a score < 5.1 kPa, 93% were stage F0 or F1.[19] Moreover, a systematic review found excellent accuracy for diagnosing the earliest stages of fibrosis.[81] If HE values suggest cirrhosis and the pretest probability is high, again no biopsy is warranted and the patient could receive appropriate cirrhotic management. For values in the gray zone, between 6 and 9 kPa, a clinician can opt to proceed with biopsy only if treatment is not planned, so as to avoid missing false negative results and the opportunity to treat a compensated cirrhotic patient. If treatment is planned, liver biopsy can be avoided.[82]

A second paper detailing an algorithm for hepatitis C staging and management offers an additional feature. For these intermediate values, a serologic panel can be added to increase the predictive value. The AST: platelet index (APRI) and Forns Index were suggested.[83] As these noninvasive markers have AUROC > 0.8 in validation studies[64] they may be especially useful in combination with HE for treatment decision-making,[56,84–86] such as a second opinion to strengthen an argument against biopsy. It is easy to imagine other scenarios in which HE can be used in lieu of biopsy, such as when biopsy is contraindicated, unavailable or not-preferred by the patient; when the clinician does not believe the interpretation of a biopsy; a baseline HE measurement is obtained in patients with biopsy F0 so that future surveillance can be carried out with HE; pregeneral surgery evaluations; and the list goes on.

CONCLUSIONS

In conclusion, there is an urgent need for noninvasive markers to quantify liver fibrosis. Hepatic elastography is a novel tool that exploits the correlation between liver stiffness and liver fibrosis. It is excellent at making the diagnosis of cirrhosis and at excluding fibrosis[87]; it is not able to discriminate between the intermediate stages of fibrosis. Several intrahepatic processes confound the accuracy of HE to gauge fibrosis, and it remains to be seen how these processes will influence future research efforts. It is conceivable that instead of absolute cutoffs, a range of values will be used for diagnosis. HE can be helpful for treatment and management decisions.[2,82,88] The era of HE used as the evaluator of the natural history of disease, both pretransplant and posttransplant, is now underway. More studies are necessary to delineate the most appropriate clinical scenarios for this useful new tool.

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