

Transient Elastography as Non-Invasive Examination of Hepatic Fibrosis

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Abstract: Over the past decade, significant advances have been made in the noninvasive assessment of liver fibrosis in patients with chronic liver disease. Transient elastography appears to be excellent in assessing liver fibrosis. For the interpretation of liver stiffness measurements, the doctor should know the disease clinically, biologically and morphologically and its parameters. In chronic liver disease, especially in chronic hepatitis C, the value of liver stiffness is strongly correlated with fibrosis stage according to the histology score. Patients with similar fibrosis but high alanine aminotransferase levels tend to have higher liver stiffness values, especially in chronic hepatitis B, and diagnostic performance for low-stage fibrosis can be affected when ALT is elevated. Transient elastography is an excellent tool for early detection of cirrhosis. Although TE cannot completely fulfill the need for liver biopsy, it can be used as an important noninvasive tool that allows the setting up of more efficient and custom management strategies for patients with chronic liver disease.

1 INTRODUCTION

Hepatic fibrosis is a structural and functional change in chronic liver disease. The process of formation of scarring occurs dynamically where chronic inflammation stimulates the production and accumulation of collagen and extracellular matrix proteins. This is one of the major prognostic factors in which the amount of fibrosis is correlated with the risk of developing cirrhosis and its complications, both with viral and non-viral causes (Younossi, 2011).

Liver biopsy is the gold standard diagnosis of evaluation of hepatic fibrosis in patients with chronic liver disease. This method is an invasive procedure, and quite expensive. Thus, it cannot be used for routine evaluation or conducted repeatedly. Therefore, a non-invasive method is required. Non-invasive methods currently used consist of laboratory testing and imaging (Cadranel, 2000).

The non-invasive diagnosis of hepatic fibrosis has gained attention over the past 10 years (Afdhal, 2007). The first generation of simple blood tests is combined with the common signs of fibrosis

indirectly into simple ratios, such as APRI and FIB-4. Subsequently, the second generation of blood test calculated is combined with logistical regression fibrosis signs, both direct and indirect markers such as Fibrotest, Fibro Meter, and Hepascore, or direct markers such as ELF scores and Fibrospect. The third step is liver stiffness evaluation by transient Elastography (Sandrin, 2003; Sterling, 2006). Transient Elastography (TE) is a method used in the assessment of patients with chronic liver diseases. Many studies have evaluated the performance of these methods for the diagnosis of fibrosis and cirrhosis, and Fibro Scan is a tool currently used by hepatologists worldwide (Fontaine, 2007).

Fibro Scan has several advantages when compared with a liver biopsy as a standard gold diagnosis. Liver biopsy, however, is an invasive procedure, expensive, has a morbidity risk and high "sampling error", because the area is smaller compared to Fibro Scan. In addition, Fibro Scan can assess the level of fibrosis as early as possible in the course of liver disease. This review article aims to discuss the advantages of Fibro Scan in hepatic fibrosis examination.

2 PRINCIPLE OF TRANSIENT ELASTOGRAPHY

Transient Elastography using Fibro Scan® (Echosens, Paris, France) is a non-invasive method for measuring liver fibrosis. An ultrasound transducer (5 MHz) probe is mounted on the vibrator axis. Vibrations of light and low-frequency amplitude (50 Hz) are transmitted from the vibrator to the network by the transducer itself, causing elastic waves that spread through the network. Meanwhile, the precision of ultrasound reflections is made to follow the propagation of the shear wave and measure its speed, which is directly related to tissue stiffness (Sandrin, 2003). The measurement results are expressed in kilopascals (kPa). The harder the tissue due to the fibrosis process, the faster the wave propagates.

TE performance only takes a few minutes, and is tolerated well by most patients. TE is performed on the right lobe of the liver, through the intercostal space, with the patient lying on the back of the decubitus with the right arm in maximum abduction. The operator, aided by an ultrasound motion picture time, place the probe at least 6 cm near the heart and is free from large blood vessels and gallbladder structure, then pushes the probe button to start measurement. Usually, 10 valid measurements should be taken to check the patient with TE. The average value of ten valid measurements is considered to represent liver elasticity. The success rate is calculated by the number of valid measurements divided by the total number of measurements. The result is immediately obtained after TE performance and expressed in kilopascals (kPa), corresponding to the median of 10 validated measurements (range 2.5-75 kPa). The validity of TE results also depends on two important parameters: (1) the interquartile range (IQR), which reflects the variability of the measures validated, and should not exceed 30% of the median value; and (2) the success rate (the success ratio of measurements for the total number of acquisitions) should be at least 60% (Castera, 2008).

The measurement of liver fibrosis is difficult to conduct in patients who are overweight or in those with narrow intercostal spaces and in patients with ascites. The failure rate ranges between 2.4% and 9.4% in several different studies. In the case of overweight or obese patients, subcutaneous fat in the thoracic region affects both elastic and ultrasound waves causing the measurement of liver stiffness to be impossible. Therefore, a specific probe is being developed for obese patients (Sandrin, 2003).

3 RESULT INTERPRETATION

In addition to the assessment of liver fibrosis, it is also important to confirm whether TE is believed to identify patients with normal chronic liver disease. However, very little research has been conducted. Roulot et al. studied a cohort with samples of 429 healthy subjects in France to establish normal TE values (5.81 ± 1.54) kPa in males and 5.23 ± 1.54 kPa in females. Normal TE values in Asia have also been reported. Fung et al. reported average TE values in 28 healthy liver donors of 4.6 kPa, and some other studies had $TE < 7.2$ kPa which meant that they did not have significant fibrosis (Fung, 2010).

4 EXAMINATION USING FIBRO SCAN

Most research on TE focuses on the ability to identify fibrosis and cirrhosis significantly, since the discovery of significant fibrosis is an indication for antiviral treatment and the occurrence of cirrhosis as the basis of surveillance programs for early detection of hepatocellular carcinoma (HCC). The current gold standard for the assessment of liver fibrosis is liver biopsy. In the calculation of TE, diagnostic accuracy is used as a comparator of the liver biopsy. The accuracy of TE is estimated by calculating the areas under the receiver operating characteristics curve (AUROC) for the prediction of each fibrosis stage based on liver biopsy, and comparing this with the other non-invasive model of AUROC values (Afdhal, 2007).

4.1 Acute Hepatitis

Three recent studies have shown that the results of TE may be influenced by increased ALT values (Coco, 2007; Arena, 2008). Coco et al. reported an increase in the liver stiffness of 1.3 to 3 times as ALT increased and returned to normal value in 10 patients with chronic hepatitis virus and acute exacerbation (9 hepatitis B). Another study reported a similar result in 18 patients with acute hepatitis virus without a history of liver disease. Also in this study, progressive normalization of liver stiffness values was observed in parallel with decreased aminotransferase levels. Finally, a high liver stiffness value in cirrhosis in 15 of 20 patients with liver damage without cirrhosis or liver cirrhosis was found on physical examination, ultrasound

examination, or liver histology (performed in 11 patients).

In acute hepatitis A, liver stiffness changes dynamically during the course of the disease. In a study of 31 patients, it was reported that the peak of liver fibrosis on day 8 after the onset of the disease was 11.9 ± 5.7 kPa, and all patients had values of less than 5.5 kPa on day 34 (Foucher, 2006). A prospective study of 60 acute hepatitis patients with varying etiology and liver stiffness values were significantly diagnosed with platelet quantity, ALT, albumin, total bilirubin and prothrombin time. The total change in bilirubin is found to be the only factor associated with changes in liver stiffness, from diagnosis to acute hepatitis recovery stage. Therefore, the interpretation of the measurement of liver fibrosis in acute hepatitis should be careful (Seo, 2010).

4.2 Hepatitis C

A large number of studies from Western countries have shown that TE values are significantly correlated with histology at the stage of fibrosis and have high diagnostic accuracy or are similar to other non-invasive methods such as Fibro Test in patients with hepatocellular carcinoma. In this study, TE results had a cut-off value of 6.2-8.7 kPa for significant fibrosis assessment, and a 9.6-14.8 kPa cut-off for cirrhosis assessment (Sirli, 2010). In South Korea, one multicenter cohort study reported TE diagnostic performance in populations with hepatocellular carcinoma. In this study, the optimal cut-off value for significant fibrosis was 6.2 kPa and that for cirrhosis was 11.0 kPa, which was more accurate than other non-invasive parameters such as aspartat amino-platelet ratio (APRI) (Kim, 2013).

Evaluation of liver stiffness evolution during and after hepatitis C treatment according to virological response is not well-known. A pilot study showed that anti-HCV treatment is associated with decreased Fibro Scan value, regardless of the virological response. In multivariate analysis, the treatment is the only independent factor associated with decreased Fibro Scan values (Vergniol, 2009).

4.3 Hepatitis B

TE diagnostic accuracy was studied in populations with chronic hepatitis B disease. In the study, TE cut-off values to predict fibrosis were significant, 6.3-7.9 kPa, with a cut-off value for cirrhosis of 9-13.8 kPa. Currently, TE is considered to have acceptable diagnostic accuracy in patients with

chronic hepatitis B disease, although the overall AUROCs data appear slightly lower than reported from CHC populations (Leroy, 2012).

In patients with hepatitis B, Transient Elastography gives similar results to those reported in hepatitis C for a significant diagnosis of fibrosis, severe fibrosis and cirrhosis. A significant diagnosis of fibrosis shows a cut-off of 7.2 kPa, with a sensitivity of 70%, specificity of 83%, positive predictive value and negative predictive value of 80% and 73% respectively. In an inactive carrier, the mean liver stiffness is significantly lower than in those with antigen-negative HBe. However, more detailed research may be required in patients with chronic hepatitis B virus (HBV) who receive antiviral treatment, since the first therapy. The type of drug to be used may be affected by the stage of fibrosis (Fung, 2010).

Patients with similar fibrosis stages but higher ALT levels tend to have higher liver stiffness values, and the results of diagnostic values for low fibrosis can be affected by high ALT values. Among patients with cirrhosis, the median of patients' liver stiffness with high ALT (16.6 kPa) is significantly higher than those with normal ALT levels (12.3 kPa). The measurement of liver stiffness below 5.0 kPa showed no liver fibrosis regardless of ALT level. For patients with normal ALT, liver stiffness measurements of 5.0-6.0 kPa will show significant fibrosis. A measurement of liver stiffness over 9.0 kPa has a high probability of fibrosis, and above 12.0 kPa has a high likelihood of cirrhosis. For patients with increased ALT, liver stiffness measurements of 5.0-7.5 kPa indicate fibrosis while a measurement of liver stiffness over 12.0 kPa has a high probability of fibrosis and measurement of liver stiffness over 13.4 kPa has a high likelihood of cirrhosis (Chan, 2009).

In general, cut-off values of cirrhosis in patients with chronic hepatitis B tend to be lower than those with chronic hepatitis C. This phenomenon can be explained by the fact that a lower amount of liver fibrosis due to hepatitis B virus tends to produce macronodular cirrhosis. In addition, doctors should also remember the effect of increased ALT, which is often found in chronic hepatitis B. Thus, TE values in populations with chronic hepatitis B should be interpreted with caution because of the false negative value (low fibrotic) and false-positive value (high ALT). In order to overcome the confounding effects of high ALT, the cut-off value is adjusted for ALT levels in patients with chronic hepatitis B (Kim, 2011).

4.5 Chronic Cholestasis

There is a strong correlation between liver stiffness and fibrosis in chronic cholestasis disease (PBC and sclerosing cholangitis). For each stage of fibrosis, it has a higher cut-off value than in chronic hepatitis C because of the nature of liver fibrosis or its cholestasis. Extrahepatic cholestasis increases liver stiffness without the occurrence of fibrosis. Liver stiffness occurs shortly before endoscopic retrograde cholangiopancreatography and 3-12 days after successful biliary drainage in patients with extrahepatic cholestasis largely due to neoplastic invasion of biliary branching. Initially, increased liver stiffness decreased in 13 of 15 patients after intervention. Drainage resulted in a decrease in bilirubin from 2.8-9.8 mg/dl, while liver stiffness was almost normal (mean: 7.1 kPa). In all patients with successful bile drainage, decreased liver stiffness is strongly associated with decreased bilirubin (Millonig, 2008).

4.6 Alcoholic Liver Disease

There is a strong correlation between hardening of the liver and liver fibrosis in alcoholic liver disease. Sensitivity, specificity, positive predictive value and negative predictive value are 80%, 90.5%, 93% and 70%, respectively, for significant fibrosis diagnosis, and 85.7%, 84.2%, 68.6% and 87.9%, respectively, for the diagnosis of cirrhosis. These results open up new perspectives in the areas of systemic alcoholic liver disease for liver fibrosis, longitudinal monitoring and as a motivational aid in the treatment of alcohol withdrawal (Nguyen-Khac, 2008).

4.7 Non-Alcoholic Liver Fatty Disease

There is only one major study evaluating Fibro Scan performance for the diagnosis of fibrosis in patients with liver metabolic disease. At a 7.9 kPa cut-off value, the sensitivity, specificity, positive and negative predictive value for severe fibrosis are 91%, 75%, 52% and 97%. Liver stiffness is not affected by liver steatosis, necroinflammation or BMI (Wong, 2010).

However, the measurement of liver stiffness is difficult in patients who are obese. When the shot is deemed unsuccessful, the machine gives no value. Assessment of liver stiffness is considered to have failed if ten shots or more do not show results. In recent studies, measurement failure occurred in 3.1% of all examinations and was independently associated with BMI above 30 kg/m², and operator

experience was below 500 trials, over 52 years old and type 2 diabetes. Therefore, a new probe, named XL probe, has been designed specifically for obese patients. It has lower and more sensitive ultrasonic transducers, more focus lengths, larger vibration amplitude and more depth for measurement below the surface of the skin. In a pilot study of 99 patients with an average BMI of 40.5 kg/m², the measurement of liver stiffness was successful (ten valid measurements) in 45% of cases with the M probe, compared to 76% of cases with the XL probe ($p < 0.001$). In total, 59% of those who could not be measured (less than ten valid measurements) with M probes could be successfully measured using the XL probe (de Ledinghen, 2010).

4.8 Liver Cirrhosis

In a meta-analysis based on nine studies, the estimation of excellent cirrhosis diagnosis was 87% sensitivity (95% CI: 84-90%), 91% specificity (95% CI: 89-92%), Positive probability ratio 11.7 (95% CI: 7.9-17.1) and negative likelihood ratio of 0.14 (95% CI: 0.10-0.20). Transient Elastography is an excellent tool for early detection of cirrhosis, regardless of the underlying disease. In patients with cirrhosis, liver stiffness ranges from 13-15 to 75 kPa. The value of liver stiffness is significantly correlated with the Child-Pugh score and with clinical parameters (history of variceal hemorrhage or ascites and hepatocellular carcinoma), biological parameters (platelets, prothrombin time, factor V, albumin and bilirubin) and other relevant parameters (esophageal varices stage 2/3, splenomegaly in ultrasonography), and the severity of liver disease. For example, the cut-off values of 27.5, 37.5, 49.1, 53.7 and 62.7 kPa have 90% sensitivity and those values are above the negative predictive value for oesophageal varices stage 2 or 3, Child-Pugh B or C, history of ascites, hepatocellular carcinoma and esophageal hemorrhage (Talwalkar, 2007).

5 CONCLUSION

Hepatic fibrosis is a structural and functional change in chronic liver disease. Transient Elastography (TE) appears to be excellent in assessing liver fibrosis. For the interpretation of liver stiffness measurements, the doctor should know the disease clinically, biologically and morphologically and its parameters. In chronic liver disease, especially in chronic hepatitis C, the value of liver stiffness is strongly correlated with fibrosis stage according to

the histology score. Patients with similar fibrosis but high alanine aminotransferase levels tend to have higher liver stiffness values, especially in chronic hepatitis B, and diagnostic performance for low-stage fibrosis can be affected when ALT is elevated.

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