

Special Article

Non-invasive evaluation of liver fibrosis using transient elastography[☆]Laurent Castera^{1,*}, Xavier Forns², Alfredo Alberti³¹*Departments of Hepatology, Hospital Saint-André & Haut Lévéque, University Hospital of Bordeaux, Bordeaux, France*²*Liver Unit, Hospital Clinic, IDIBAPS, Ciberehd, Barcelona, Spain*³*Department of Clinical and Experimental Medicine and Venetian Institute of Molecular Medicine (VIMM), University of Padova, Padova, Italy*

Transient elastography (TE, FibroScan[®]) is a novel non-invasive method that has been proposed for the assessment of hepatic fibrosis in patients with chronic liver diseases, by measuring liver stiffness. TE is a rapid and user-friendly technique that can be easily performed at the bedside or in the outpatient clinic with immediate results and good reproducibility. Limitations include failure in around 5% of cases, mainly in obese patients. So far, TE has been mostly validated in chronic hepatitis C, with diagnostic performance equivalent to that of serum markers for the diagnosis of significant fibrosis. Combining TE with serum markers increases diagnostic accuracy and as a result, liver biopsy could be avoided for initial assessment in most patients with chronic hepatitis C. This strategy warrants further evaluation in other aetiological types of chronic liver diseases. TE appears to be an excellent tool for early detection of cirrhosis and may have prognostic value in this setting. As TE has excellent patient acceptance it could be useful for monitoring fibrosis progression and regression in the individual case, but more data are awaited for this application. Guidelines are needed for the use of TE in clinical practice.

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Keywords: Transient elastography; FibroScan; Liver fibrosis; Reproducibility

1. Introduction

The prognosis and management of chronic liver diseases largely depend on the extent and the progression of liver fibrosis. For instance, in patients with chronic hepatitis C, the leading cause of chronic liver disease worldwide, precise staging of hepatic fibrosis is paramount as fibrosis is the most important predictor of dis-

ease outcome and influences the indication for antiviral therapy [1,2]. Histopathological examination of a liver specimen obtained by percutaneous biopsy has traditionally been considered as the gold standard for evaluating hepatic fibrosis [3]. However, liver biopsy is an invasive and painful procedure, often with poor patient acceptance and also carries a significant, although small risk of life-threatening complications [4,5]. The accuracy of liver biopsy for assessing fibrosis has also been questioned, due to sampling errors and intra- and inter-observer variability that may lead to over or underestimation of fibrosis stage [6,7]. Even when an experienced physician performs liver biopsy and an expert pathologist interprets the results, liver biopsy has up to a 20% error rate in disease staging [8]. In addition, it is certainly not the ideal procedure for serially repeated assessment of disease progression.

These findings thus emphasize the need for non-invasive tools that accurately measure the degree of liver fibrosis. Ideally, a non-invasive marker of liver fibrosis

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Abbreviations: TE, transient elastography; ALT, alanine aminotransferase levels; HBV, hepatitis B virus; AUROC, area under the ROC curve; CI, confidence interval.

should be liver-specific, easy to perform, reliable and inexpensive. In addition, it should be accurate not only for the grading of fibrosis, but also for monitoring disease progression and treatment efficacy. A variety of surrogate markers have been evaluated for their ability to assess liver fibrosis, mostly in patients with chronic hepatitis C [9–12]. The latest technological advance in this setting is the measurement of liver stiffness by means of transient elastography (TE).

This special article aims at reviewing the data currently available regarding TE performance in assessing stage and progression of liver fibrosis, and compares it to the other non-invasive methods that have become available for this purpose. This review will also discuss the advantages and limits of TE and perspectives for its rational use in clinical practice.

2. Transient elastography

2.1. Principle

TE, using FibroScan[®] (Echosens, Paris, France), is a novel non-invasive method that has been proposed for assessment of liver fibrosis by measuring liver stiffness [13]. Briefly, an ultrasound transducer probe is mounted on the axis of a vibrator (Fig. 1A). Vibrations of mild amplitude and low frequency (50 Hz) are transmitted by the transducer, inducing an elastic shear wave that propagates through the underlying tissues. Pulse-echo ultrasound acquisition is used to follow the propagation of the shear wave and to measure its velocity, which is directly related to tissue stiffness (the elastic modulus E expressed as $E = 3\rho V^2$, where V is the shear velocity and ρ is the mass density (constant for tissues)): the stiffer the tissue, the faster the shear wave propagates (Fig. 1B). TE measures liver stiffness in a volume that approximates a cylinder 1 cm wide and 4 cm long, between 25 mm and 65 mm below the skin surface. This volume is at least 100 times bigger than a biopsy sample, and is therefore far more representative of the hepatic parenchyma.

2.2. Interpretation of results

TE is painless, rapid (less than 5 min) and easy to perform at the bedside or in the outpatient clinic. The examination is performed on a non-fasting patient lying flat on his/her back, with the right arm tucked behind the head to facilitate access to the right upper quadrant. The tip of the probe transducer is placed on the skin between the rib bones at the level of the right lobe of the liver where liver biopsy would be performed. Once the measurement area has been located, the operator presses the probe button (shot) to start an acquisition. The software determines whether each measurement is

successful or not. When a shot is unsuccessful, the machine does not give any reading. Results are expressed in kiloPascals (kPa) and correspond, according to the manufacturer's recommendations, to the median of 10 validated measurements. Liver stiffness values range from 2.5 to 75 kPa. The results are immediately available and are operator-independent [14]. The examination can be performed by a nurse after a short learning curve (about 100 examinations) [15].

The validity of TE results also depends on two important parameters: (1) the interquartile range (IQR), which reflects the variability of the validated measures, and should not exceed 30% of the median value [16]; (2) the success rate (the ratio of the number of successful measurements to the total number of acquisitions) should be at least 60%.

The clinical interpretation of TE results should be always in the hands of an expert clinician and should be made having information regarding patient demographics, disease aetiology and essential laboratory parameters at his/her disposal.

2.3. Limitations and reproducibility

Liver stiffness measurements can be difficult in obese patients or in those with narrow intercostal space and impossible in patients with ascites [13]. Failure rates range between 2.4% and 9.4% in the different studies [13,14,17–21]. According to our experience in 2114 examinations, liver stiffness could not be measured in 4.5% of cases [22]. In multivariate analysis, the only factor associated with failure was a body mass index above 28 (odds ratio 10.0; 95% confidence interval 5.7–17.9, $P = 0.001$). However, with more experience, we think that rather than body mass index, a fatty thoracic belt is a limiting factor for the success rate. Indeed, in overweight or obese patients, the fatty thoracic belt attenuates both elastic waves and ultrasound making liver stiffness measurement impossible. Specific probes are being developed for obese patients.

Three recent studies suggested that TE results may be influenced by ALT flares [21,23,24]. Coco et al. [21] reported a 1.3- to 3-fold increase in liver stiffness values at the time of ALT flares with a progressive return to baseline values afterwards in 10 patients with chronic viral hepatitis and acute exacerbations (9 with hepatitis B). Arena et al. [23] reported similar results in 18 patients with acute viral hepatitis without a history of liver disease. Also in this study, progressive normalization of liver stiffness values was observed in parallel with the decrease of aminotransferase levels. Finally, Sagir et al. [24] reported high liver stiffness values suggestive of cirrhosis in 15 out of 20 patients with acute liver damage without any signs or liver cirrhosis at physical examination, ultrasound examination, or liver histology (performed in 11 patients). In six patients in whom a

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