Transient elastography in chronic viral hepatitis: a critical appraisal

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Even with all the heated discussion about the value of liver biopsy, it remains the gold standard method for the assessment of liver fibrosis and the severity of chronic liver diseases.[1] Histological analysis of liver tissue still provides invaluable information about three key issues for the management of patients with liver diseases: diagnosis, prognosis and therapeutic decisions. In the context of chronic infection with hepatitis C virus (HCV) or hepatitis B virus (HBV), evaluation of the stage of liver fibrosis is of major importance. Additional information can also be provided, such as the pattern of liver fibrosis, grading of necroinflammatory activity and the presence of steatosis and hepatic iron overload. These and other histological findings are highly relevant in clinical practice, because they not only allow the clinician to infer on the dynamics of fibrogenesis (whether lesions are ancient or progressive), but also permit the identification of associated liver diseases that can potentially alter the natural history of chronic viral hepatitis and impair the efficacy of therapy.

Nevertheless, liver biopsy is a costly and invasive technique with associated mortality and morbidity, well documented in both retrospective and prospective studies.[2 3] A typical biopsy fragment represents only 1/50 000 of the organ and most chronic liver diseases exhibit a heterogeneous distribution of hepatic fibrosis. Therefore, histopathological analysis of liver tissue is susceptible to variability in interpretation, being significantly influenced by the quality of the fragment (adequate length and number of portal tracts) and by the expertise of the pathologist.[4 5]

In a world with an imperfect gold standard model, several non-invasive approaches have been proposed to estimate liver fibrosis in patients with liver diseases, particularly in those chronically infected by HCV and HBV.[6] Basically, there are three types of non-invasive tests for the assessment of hepatic fibrosis: serum fibrosis markers; conventional imaging studies and innovative physical techniques. Various serum tests reflecting modifications on the extracellular matrix (direct biomarkers) or changes in hepatic function (indirect biomarkers) have been proposed, either isolated or combined in panels. However, many of those are neither readily available nor widely validated, particularly in special populations (eg, HIV or HBV co-infections). Conventional imaging methods such as ultrasound, CT or MRI have high specificity for the diagnosis of liver cirrhosis, but they all show a low sensitivity for the identification of the early stages of hepatic fibrosis.[7 8] Novel methods have recently been proposed to evaluate liver fibrosis, such as real-time elastography, acoustic radiation force impulse imaging (ARFI), magnetic resonance elastography (MRE) and transient elastography (TE).[9–14] In comparison with TE, real-time elastography exhibited lower diagnostic performance, and ARFI and MRE showed similar or even better accuracies (in the case of MRE) for predicting both significant fibrosis and cirrhosis. From a clinical point of view, the incorporation of elastography measurement with conventional imaging devices has the advantage of providing an all-in-one non-invasive assessment of fibrosis. However, these techniques require highly specialised operators and should be considered experimental tools, because standardisation and reproducibility data are still lacking. In contrast, among all liver elastography-based methods, TE is by far the most validated method for the assessment of fibrosis in patients with chronic liver diseases.

Considering the growing knowledge in the field of non-invasive assessment of liver fibrosis and to incorporate TE properly into day-to-day clinical practice, it is imperative to consider its principles, clinical applications and limitations for the management of patients with chronic hepatitis C or chronic hepatitis B.

PRINCIPLES OF TRANSIENT HEPATIC ELASTOGRAPHY

TE, as assessed by FibroScan (Echosens, Paris, France), is a painless non-invasive method to measure liver stiffness. The test is simple, fast and can be easily carried out in both inpatient and outpatient settings. It has been tested in a variety of liver diseases, including acute and chronic viral hepatitis, autoimmune and metabolic liver diseases, both in adults and in children. The method is based on the unidimensional TE, a technique that uses elastic waves and low frequency ultrasounds (see Castéra *et al*[15] for further details). Briefly, low amplitude vibrations produced by the probe are transmitted to liver tissue and ultrasound pulses follow and measure the velocity of propagation of elastic waves inside the parenchyma. The velocity of propagation is directly related to elasticity: the harder the tissue, the faster the propagation of elastic waves. The final result represents the median of all valid acquisitions and ranges from 2.5 to 75.0 kPa. Within this range, several studies have tried to identify cut-off values associated with two clinically relevant endpoints for assessing liver fibrosis in viral hepatitis: significant fibrosis (at least septal fibrosis), the classical threshold for indicating antiviral therapy, and cirrhosis, which triggers screening for portal hypertension and hepatocellular carcinoma (HCC).

TE IN CHRONIC HEPATITIS C

Although TE has been evaluated in several non-viral chronic liver diseases,[16–19] it was initially proposed and subsequently validated in patients with chronic hepatitis C.[14 20–23]

Several studies have shown significant positive correlation between TE and the stage of hepatic fibrosis, as evaluated by the METAVIR score system,[20–22] as well as by computer-assisted morphometric image analysis.[23] Castéra *et al*[20] evaluated and compared the performance of FibroScan, FibroTest (Biopredictive, Paris, France) and the AST-to-platelet ratio index (APRI) in 183 HCV patients. The areas under the curve (AUROC) of FibroScan, FibroTest and APRI for the diagnosis of significant fibrosis (as defined by ≥F2) were 0.83, 0.85 and 0.78, respectively, and to estimate the presence of cirrhosis (F4), the AUROC were 0.95, 0.87 and 0.83,

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respectively. TE measurement showed similar diagnostic performance to predict the stage of liver fibrosis when using computerised morphometry, with AUROC of 0.88 and 0.90 to identify F2 or greater and F4, respectively.[23] A French study with 298 HCV patients compared the performance of FibroScan, FibroTest, APRI, Lok index, platelet count, prothrombin index and AST/ALT ratio for the early detection of cirrhosis. In that study, TE was the most accurate method for predicting cirrhosis (AUROC TE 0.96 vs FibroTest 0.82, Lok index and APRI 0.80, platelet count 0.79, prothrombin index 0.73, AST/ALT ratio 0.61; $p<0.0001$).[24] One can thus conclude that FibroScan shows a similar performance for predicting significant fibrosis and higher accuracy to identify liver cirrhosis, compared with serum markers of fibrosis. A recent study confirmed the superiority of TE over other serum biomarkers in 1839 French patients with chronic viral hepatitis, being highly accurate for excluding liver cirrhosis in HCV patients (negative predictive value (NPV) of 95.3% using a cut-off of 12.9 kPa).[25] As expected, TE exhibited a lower performance for predicting significant fibrosis (positive predictive value (PPV) of 67.9%, with a low cut-off of 5.2 kPa). A meta-analysis of 50 studies evaluating TE for the diagnosis of liver fibrosis in chronic liver disease of various aetiologies confirmed the lower performance of TE in estimating F2 or greater, with mean AUROC for predicting significant fibrosis, advanced fibrosis and cirrhosis of 0.84, 0.89, and 0.94, respectively.[26] Even though it has been suggested that TE would be useful to rule out significant fibrosis, the classic cut-off value of 7.1 kPa provided NPV of only 48% and 61.4% to exclude stages F2 or greater in the studies by Castéra *et al*[20] and by Degos *et al*[25] In fact, in this last study, even a lower cut-off value of 5.2 kPa exhibited a NPV of only 66.1%. Therefore, in order to increase the accuracy for estimating liver fibrosis (particularly to exclude significant fibrosis), strategies combining TE with serum markers have been proposed.[27 28] Even if the synchronous combination strategy of TE plus FibroTest and TE plus Fibrometer has succeeded in increasing the overall diagnostic performance for predicting significant fibrosis, only the combination TE plus Fibrometer significantly increased the NPV to approximately 95%.[28] Therefore, further studies are needed before using TE (isolated or in combination) to exclude significant fibrosis with certainty. In addition, the combination approach does not seem to increase TE accuracy significantly in predicting cirrhosis.[27] Therefore, the beneficial impact of combining non-invasive markers is still a matter of dispute.

The most validated TE cut-off points are 7.1 kPa to discriminate patients with significant fibrosis and 12.5 kPa to identify those with cirrhosis.[20 24 29] Even though the studies by Degos *et al*[25] and Friedrich-Rust *et al*[26] have suggested slightly different cut-offs, they exhibited overall accuracies similar to the classic cut-offs. It should be noted, however, that using 12.5 kPa as the cut-off, TE constantly shows low PPV to predict the presence of cirrhosis (only 52% in the largest study to date).[25] On the other hand, TE values of 14.6 kPa or greater exhibited a PPV of 90% to predict the presence of liver cirrhosis, with a positive likelihood ratio of 35.5.[21 24] Therefore, this higher cut-off could be more appropriate to predict cirrhosis.

TE was also evaluated in special populations of patients with chronic hepatitis C, such as HCV/HIV co-infection[30 31] and post-transplant hepatitis C,[32–35] with accuracy equivalent to that observed in the general population of HCV patients.

In addition to estimating the stage of hepatic fibrosis, some authors have proposed TE to stratify patients with cirrhosis further through the association of specific cut-offs with liver dysfunction and with the risk of developing portal hypertension, liver-related complications and HCC. In a study with 711 HCV patients, the cut-off points of 27.5, 37.5, 49.1, 53.7 and 62.7 kPa showed a NPV exceeding 90% for the presence of oesophageal varices of grades II or III, score Child–Pugh B or C and previous episodes of ascites, HCC and oesophageal varices bleeding, respectively.[36] Except for HCC (see below), additional prospective studies are needed to determine whether TE could be used to predict which patients with cirrhosis will develop decompensated disease. Specifically regarding portal hypertension, several studies have shown a positive correlation between TE and the hepatic venous pressure gradient (HVPG), and found an association between high TE values and the presence of oesophageal varices.[24 32 37–40] Nevertheless, several different cut-off values were used and many of those studies have found weak correlation coefficients, particularly among patients with high HVPG (>10 mm Hg). It should be emphasised that these individuals with significant portal hypertension are under greater risk of hepatic decompensation.[41] Taken together, these data indicate that the relationship between TE and HVPG is insufficiently linear to allow the identification of clinically useful cut-offs to restrict endoscopic screening. Therefore, at present, TE cannot replace endoscopic screening for varices in patients with cirrhosis.

Masuzaki *et al*[42] prospectively evaluated 866 HCV patients during a mean follow-up of 3 years and found a noteworthy association between TE and the risk of developing HCC. Individuals with TE measurement greater than 10 kPa exhibited a significantly higher risk of HCC. This cut-off of 10 kPa is close to the cut-off associated with advanced fibrosis or cirrhosis, stages obviously associated with a higher risk of HCC. However, more studies performed in different populations and careful cost-effectiveness studies should be performed before concluding that HCC screening could be safely restricted to individuals with high TE.

Monitoring the progression of liver fibrosis after antiviral therapy is another potential application of TE. Vergniol *et al*[43] showed a significant reduction of TE in patients treated with pegylated interferon and ribavirin, regardless of achieving sustained virological response (SVR). A Japanese study performed FibroScan at baseline, at the end of therapy and 48 and 96 weeks after the end of therapy in 145 HCV subjects.[44] In that study, patients with SVR showed a significant reduction in liver stiffness during follow-up. Interestingly, this was also observed among those without SVR but with biochemical response. In addition, in a study conducted by our group with 114 HCV subjects with advanced fibrosis or cirrhosis (F3/F4), SVR patients exhibited lower TE values compared with non-responders during follow-up after treatment, with a progressive decrease in TE values over time.[45] Nonetheless, in spite of these interesting findings, it is not clear if the reduction observed after interferon-based therapy reflects a true decrease in liver fibrosis or a decline in necroinflammatory activity. It also remains to be determined whether the post-treatment reduction in TE measurements improves outcome.

The potential uses for TE measurements in chronic hepatitis C patients are listed in table 1.

TE IN CHRONIC HEPATITIS B

In contrast to chronic hepatitis C, there are few studies with appropriate

Table 1 Proposed indications for the use of TE in patients with compensated chronic hepatitis C and B

Purposes	Indications
Baseline assessment and therapeutic decisions*	Alternative to liver biopsy for subjects with contraindications to the procedure or for patients who refuse to be biopsied.
	Alternative to liver biopsy for patients without conditions with potential impact on the accuracy of TE measurement and/or on the outcome of viral infection (alcohol abuse, overweight, insulin resistance, HIV infection) if: (a) TE ≥14.6 kPa in HCV patients†; or (b) TE ≥12.0 kPa in HBV patients with normal ALT‡.
Follow-up§	Annual TE measurements for patients without indication for antiviral therapy. Consider earlier liver biopsy in case of unexplained TE elevation.
	Annual TE measurements for all patients during (HBV) or after (HBV or HCV) antiviral therapy. Consider earlier liver biopsy in case of unexplained TE elevation.

*Appropriate screening for oesophageal varices and hepatocellular carcinoma is recommended.
†The impact of ALT levels on the accuracy of TE in HCV infection remains to be defined.
‡Increased ALT levels seem to increase TE values.
§After baseline assessment of liver fibrosis with liver biopsy and TE measurement.
HBV, hepatitis B virus; HCV, hepatitis C virus; TE, transient elastography.

methodology on the accuracy of TE in patients with chronic hepatitis B.[46–49] In a multicentre French study, Marcellin *et al*[49] prospectively evaluated 173 HBV patients and found AUROC of 0.81 (95% CI 0.73 to 0.86) for predicting fibrosis stage F2 and greater, and 0.93 (95% CI 0.82 to 0.98) for estimating the presence of F4. Maximising the sum of sensitivity and specificity, the cut-off points of TE to predict the presence of significant fibrosis (≥F2) and cirrhosis (F4) were 7.2 kPa and 11.0 kPa, respectively. Only one other study[46] has used TE to predict fibrosis of F2 or greater, using 8.3 kPa as a cut-off point, a value close to that found by Marcellin *et al*.[49]

In different studies, the cut-off points for estimating the presence of F4 vary significantly (ranging from 9.0 to 14.0 kPa). This discrepancy could be explained by the different populations studied and, at least partly, by interferences in TE measurement exerted by a macronodular pattern of cirrhosis and by the fluctuation of hepatic necroinflammatory activity (often expressed as exacerbations in serum aminotransferases levels), features frequently found in chronic HBV infection. Based on this concept, an algorithm has been proposed to adjust the interpretation of TE values according to ALT levels, in which values less than 6.0 kPa and less than 7.5 kPa would accurately predict the absence of advanced fibrosis or cirrhosis in patients with serum ALT levels inferior to the upper limit of normality (ULN) and in patients with ALT activity between one and five times the ULN, respectively.[48] Likewise, TE values greater than 9.0 kPa and greater than 12.0 kPa would predict the presence of advanced fibrosis or cirrhosis in patients with normal ALT and in those with ALT one to five times the ULN. Additional studies are needed to confirm whether this algorithm significantly improves the accuracy of TE measurement for the estimation of advanced fibrosis or cirrhosis in HBV carriers.

Another relevant issue is to determine whether TE exhibits diagnostic performance similar to that seen in patients with chronic hepatitis C. It should be noted that in HBV infection, a more precise fibrosis staging is advisable for therapeutic decisions, particularly to select candidates for antiviral treatment (septal fibrosis (F2) is usually required), as well as to decide the best drug to be used (interferon is typically not indicated for patients with cirrhosis). A recent study performed by our group analysed and compared the diagnostic performance of TE for the assessment of liver fibrosis in 202 HBV patients and in 363 HCV patients.[29] The AUROC of TE for predicting F2 or greater were 0.867±0.026 and 0.868±0.019 in HBV and HCV patients, respectively (p=0.975). For predicting F3 or greater, AUROC were 0.896±0.016 and 0.894±0.020 in HBV and HCV patients, respectively (p=0.938). These results suggest that TE exhibits similar diagnostic performances in HBV infection compared with HCV patients.

Only one study has evaluated TE in HIV/HBV co-infected subjects, showing a significant correlation between liver stiffness and the METAVIR fibrosis score.[50] Additional studies are necessary in special populations of HBV patients, such as transplant recipient patients and individuals under chemotherapy. Similarly, studies assessing the prognostic value of TE regarding liver-related complications are lacking. Fung *et al*[51] evaluated 528 hepatitis B e antigen-negative patients divided into two groups by using a cut-off point of 10 kPa. Subjects with TE of 10 kPa or greater exhibited higher cumulative incidences of HCC and liver-related mortality after 3 years of follow-up (9% vs 0%, p<0.001; and 4% vs 0%, p=0.001, respectively).

TE measurement has potential application in individuals in the immunotolerant phase of HBV infection and for distinguishing inactive carriers from patients with low replication hepatitis B e antigen-negative chronic active hepatitis B. However, few studies have addressed these populations (none with immunotolerant patients), and specific TE cut-off values are still a matter of debate.[52 53]

TE could also be used for monitoring disease progression after antiviral therapy. Vigano *et al*[54] evaluated 118 HBV patients treated with entecavir (40% of patients with cirrhosis) and found a significant decrease of TE from median values of 10 to 6.9 kPa (p<0.0001). Noteworthily, 63% of patients with baseline TE values greater than 12.5 kPa switched to a TE value of less than 12.5 kPa in the follow-up. Similarly to HCV patients, it is not yet clear if this reduction reflects fibrosis regression.

The recommended uses of TE for the management of chronic hepatitis B are shown in table 1.

LIMITATIONS OF TE

Technical issues

Between 2% and 16% of FibroScan examinations cannot be considered for patient management, with TE values that are neither valid nor interpretable. Complete failure of TE examinations is considered when no valid results are obtained after 10 shots or more. There are three criteria that define unreliable TE results, when examinations do not meet the manufacturer's recommendations: (1) insufficient number of valid measurements (<10 valid shots); (2) success rate (ratio of valid shots to the total number of shots) less than 60%; (3) IQR greater than 30%. A prospective study including 13 369 examinations assessed the frequency and the predictive factors related to TE failure and unreliable results.[55] TE failure was associated with body mass index (BMI) greater than 30 kg/m^2, operator inexperience, patient's age greater than 52 years and type 2 diabetes. Unreliable TE results were related to the same parameters and also to female gender and arterial hypertension.

Some authors have suggested that no learning curve is required to perform TE measurements,[56] and others have proposed that a rapid training of only 50 examinations

would be needed.[57] However, these studies included small samples and did not entirely comply with the manufacturer's quality criteria for TE evaluation. Moreover, the aforementioned study by Castéra and colleagues[55] observed that operator experience of less than 500 examinations not only affected the success rate but also the IQR ratio. The IQR reflects the variability of validated acquisitions and is a crucial factor for the reproducibility of TE.[58 59] Although an IQR ratio less than 30% is recommended, a ratio less than 21% of the final median value is associated with a higher accuracy of FibroScan for the diagnosis of significant liver fibrosis, with higher IQR values being associated with overestimation of TE measurements.[60]

TE measurement by FibroScan is a reproducible test, with high intra and interobserver agreement, with a coefficient of interobserver agreement of 0.980 (95% CI 0.977 to 0.987).[58] Another study, however, observed lower reproducibility for patients with TE values of less than 9 kPa.[61] Gender, age and the aetiology or severity of liver disease does not seem to affect the reproducibility of the method. However, reproducibility can be reduced in the presence of BMI of 25 kg/m^2 or greater, significant steatosis (≥25% of hepatocytes), liver fibrosis stage less than 2 (METAVIR) and in individuals with narrow intercostal spaces.[58]

Currently, TE examination is contraindicated in pregnant women, because there are no studies confirming the safety of the procedure in this context. Moreover, it is not recommended to perform the procedure in patients with ascites, because it can affect the transmission of the elastic wave, preventing adequate TE measurement.

Patient-related issues

The studies by Corpechot *et al*[62] and by Sirli *et al*[63] failed to identify a significant influence of BMI on TE. Roulot and colleagues[64] evaluated TE in 429 individuals without any signs of liver disease and found higher TE values among subjects with a BMI greater than 30 kg/m^2 (6.23±0.20 kPa), compared with those with a BMI less than 25 kg/m^2 (5.44±0.11 kPa), even after adjusting for age, gender and aminotransferases and ferritin serum levels. However, it is interesting to note that this correlation was not linear, because individuals with a BMI between 25 and 30 kg/m^2 presented with a lower mean TE than those with a BMI less than 25 kg/m^2. Moreover, in that study, in a logistic regression model including age, gender, BMI and serum levels of ALT, AST, GGT and ferritin, the presence of the metabolic syndrome was the sole variable independently associated with higher TE. Likewise, Colombo *et al*[65] observed a positive association between TE and the detection of steatosis on ultrasound, independently of BMI. Interestingly, the presence of important components of the metabolic syndrome (obesity, hypertension and diabetes) and the metabolic syndrome itself were independently associated with both TE failure and unreliability in multivariate analyses performed in the large cohort studied by Castéra *et al*.[55] Nonetheless, in this study, when BMI was replaced by waist circumference in the model, the other components of the metabolic syndrome were not retained in the final model, and only large waist circumference remained as an independent predictor of unreliable results. This finding suggests that prehepatic fat thickness could be the essential factor behind the poorer performance of TE in individuals with metabolic syndrome. Therefore, although unreliable TE measurements do seem to be more frequent among patients with metabolic syndrome, additional studies are needed in order to define the real impact of each of its components on TE measurement.

As an attempt to overcome the lower diagnostic performance of FibroScan in overweight patients, a new probe has been developed, with a 2.5 MHz ultrasonic transducer and a new electrodynamic vibrator, able to perform deeper measurement of TE, between 35 and 75 mm below the skin. As specified by the manufacturer, this new probe is indicated for individuals with a BMI greater than 30 kg/m^2, particularly for those with subcutaneous thickness greater than 2.5 cm and thoracic perimeter greater than 110 cm. However, further studies are needed to elucidate the real accuracy gain from using this new probe.

It should also be noted that TE values may be influenced by confounding factors such as significant hepatic inflammation (reflected as ALT flares),[46 66] extrahepatic cholestasis[67] and liver congestion.[68] Therefore, in those settings, TE results should be interpreted with caution, because liver stiffness could be overestimated.

CONCLUSIONS

The development of TE for predicting the stage of fibrosis is an important advance in the management of chronic liver diseases, especially in patients with chronic hepatitis C or chronic hepatitis B. TE measurement, along with clinical and laboratory parameters, provides relevant and reasonably accurate data about the severity of liver disease, and allows non-invasive monitoring of fibrosis progression. TE (also ARFI and MRE in the near future) can reduce the need for performing liver biopsy. However, given the complexity of chronic viral hepatitis, liver elastography methods cannot completely replace histological evaluation, but should act as complementary tools in the management of these patients.[69 70]

In chronic hepatitis C, the relationship between TE, BMI, steatosis and the metabolic syndrome remains controversial, and it is expected that future studies with TE will clarify this issue. Additional studies are also needed to define and validate TE cut-offs with adequate discriminatory power for predicting the presence of significant/advanced liver fibrosis in patients with chronic HBV infection according to ALT levels. It should also be noted that, whatever the population studied or the probe used, the operator must receive appropriate training, in order to optimise the diagnostic performance of the method. Whatever the context, the interpretation of the results of future studies should be made in the light of a minimum of standards of methodological rigour, in order to extrapolate their findings to day-to-day clinical practice adequately.

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