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REVIEW ARTICLE

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Elastography assessment in patients with chronic HCV infection

L. Abenavoli, G. Addolorato, L. Riccardi, A. Gasbarrini, G. Gasbarrini, G. L. Rapaccini

Istituto di Medicina Interna, Università Cattolica del S. Cuore, Roma, Italy

Correspondence to:
Dott. Ludovico Abenavoli, Istituto di Medicina Interna, Policlinico 'A. Gemelli', Università Cattolica del Sacro Cuore, L.go Gemelli 8 00168 Roma, Italy
Tel.: + 39 339 8666533
Fax: + 39 06 35502775
Email: l.abenavoli@yahoo.it

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SUMMARY

Introduction: Liver fibrosis (LB) assessment plays an important role in hepatology. A common characteristic of all chronic liver diseases is the occurrence and progression of fibrosis towards cirrhosis. Besides its plain interest for prognosis purposes, determining the fibrosis reveals the natural history of the disease and the risk factors associated with its progression to guide the antifibrotic action of different treatments. **Discussion:** Today, in clinical practice there are three available methods for the evaluation of LB. Biopsy, which is still considered as the 'gold standard' method. Serological markers and their mathematical combination are suggested in the last years in alternative to LB. More recently, transient elastography (TE) was proposed. TE is a simple and noninvasive method for measuring liver stiffness. This technique is based on the progression speed of an elastic shear wave within the liver. **Conclusions:** Currently, there are just a few studies capable of evaluating the TE effectiveness in chronic liver diseases, mainly in patients infected with hepatitis C virus (HCV). Its application must also be studied in the monitoring of patients suffering from chronic HCV infection and subjected to a treatment that can modify their degree of liver fibrosis. The results of TE must be interpreted according to the clinical background of the specialist.

Review Criteria
MEDLINE and manual searches were combined. The key words 'fibroscan', 'transient elastography' and 'HCV' were used. This review is performed according to literature data.

Message for the Clinic
Transient elastography (TE) could be a technique adapted to monitor the progression of liver disease. However, TE results must be interpreted according to the background of clinical examination, laboratory, sonography, endoscopic results and liver histology.

Introduction

In chronic liver diseases, liver biopsy (LB) followed by histological analysis, is considered the 'gold standard' technique for evaluation of the liver damage, because it confirms clinical diagnosis, assesses the severity of necroinflammatory activity and fibrosis, evaluates possible concomitant diseases and guides therapeutic interventions (1,2). This is particularly true in patients with chronic HCV infection, which is the leading cause of cirrhosis in western countries. However, the use of LB has several limitations: physical and mental discomfort in patients that may lead to a significant percentage of refusals, non-negligible morbidity (one in every 1000 patients) and occasional mortality (one in 10,000 patients) (3). Fibrosis is evaluated by histological semi-quantitative scores, among which the METAVIR index is the most used (4). It is able to detect different degrees of fibrosis from F0 (absence of fibrosis) to F4 (cirrhosis) and shows a better intra- and inter-observer reproducibility regarding others scales (i.e. Knodell, Ishak and Scheuer). Histological fibrosis scores do not provide a dynamic picture of the liver disease, but only information about the diagnosis and prognosis, such as the necroinflammatory activity and the presence of steatosis. Moreover, these scores do not have the power to assess small changes in the degree of liver fibrosis, e.g. in the course of an antiviral treatment. Besides, this technique is known to have serious limitations. Finally, its accuracy in assessing fibrosis is questionable, as reproducibility is poor because of sampling errors, and even in case of adequately sized specimens intra-observer and inter-observer discrepancies have been found (4–6). Over recent years many research groups have been working to develop noninvasive methods capable of detecting and quantifying liver fibrosis. Different biochemical markers of fibrosis along with their mathematical combinations have been reported in literature, in particular for chronic hepatitis C virus (HCV) infection (7,8). A good accuracy to distinguish mild fibrosis from cirrhosis was achieved by algorithms using multiple measures. More recently, the assessment of liver fibrosis by a noninvasive method based on physical measurements, called transient elastography (TE) (FibroScan; Echosens, Paris, France), has been proposed (9,10).

Transient elastography assessment

The elasticity of a body is defined as the ability of the body to deform itself under the action of a mechanical force. The elasticity of a tissue can be estimated on the basis of the speed of propagation of a transverse shear elastic wave. The higher the speed of propagation of that wave, the higher the stiffness of the tissue. TE measures such speed of propagation in relatively homogenous organs such as the liver, by using ultrasound pulses to localise the shear elastic wave at different times (9). The measuring device is equipped with a probe consisting of an ultrasonic transducer mounted on the axis of a vibrator. A low frequency at 50 Hz and mild amplitude vibration, referred to as 'shots', is transmitted from the vibrator to the tissue by the transducer itself. This vibration induces an elastic shear wave which propagates through the tissue. In the meantime, ultrasonic acquisitions are performed by an echographic transducer, using a frequency at 3.5 MHz, determines the propagation of the shear wave (9). The propagation speed is expressed in kPascals (kPa). The probe is applied perpendicularly to the skin (with a little gel film) through one of the right side intercostal spaces along the mid-axillary line. The measurement of the speed is taken along a cylinder of tissue ranging from 25 to 65 mm of depth under the skin. This corresponds to a volume of liver tissue approximately 100 times greater than that of an LB specimen and represents about 1% of the total organ volume. The examination is noninvasive and can be performed on ambulatory patients, in an outpatient setting or at the bedside of a hospitalised patient. TE can be performed indifferently by hepatologists or medical staff (physician, resident, medicine student, nurse) after a single training session provided by a specifically certified trainer. Results of the measurements range from 1.3 to 75.4 kPa (9). A panel discussion is in progress to define the number of necessary acquisitions to realise a measurement and the successful percentage requested to accept such measurement (11,12). The manufacturer currently recommends that fibrosis score should be established from the median value of at least 10 successful acquisitions, with the rate of valid measures always higher than 50%. The intra- and inter-observer coefficients of variation are 3.2% and 3.3%, respectively, indicating very good reproducibility and operator independence (9). Recently an Italian group have conducted a reproducibility study, in 200 patients with chronic liver disease of different aetiologies (12). Intra- and inter-observer agreement was analysed using the intra-class correlation coefficient and correlated with different patient and liver disease-related covariates. The authors concluded that TE is both a reliable and a highly reproducible noninvasive method for assessing hepatic fibrosis in chronic liver disease patients, being characterised by an overall very high inter- and intra-observer agreement (12). However, the TE reproducibility is significantly reduced in patients with steatosis, increased BMI and lower degrees of hepatic fibrosis (11). The measurement failure rate is included between 5% and 10%. The presence of obesity, fatty thoracic belt, ascites or reduced intercostal spaces are the main factors related to the measurement failure (11–13). Elasticity depends not only on the building of molecular blocks of collagen and their structural organisation (septa), but also on other factors, such as the type and extent of the inflammatory infiltrate of the septa (14–16). The role of steatosis in this context is still controversial (16,17).

Elastography in chronic hepatitis C infection

The statistical analysis of data obtained in large studies on patients with HCV infection shows that elasticity is directly correlated with the degree of hepatic fibrosis. Ziol et al. (14) enrolled 327 patients infected with HCV, to compare TE with LB. On the basis of their chosen tradeoffs between sensitivity and specificity, they proposed 8.8 kPa as a cut-off for a fibrosis equal to or greater than F2 and 14.6 kPa for cirrhosis (Table 1). The areas under receiver operation characteristic (ROC) curve were 0.79 [95% confidence interval (CI): 0.73–0.84] for $F \geq 2$, 0.91 (0.87–0.96) for $F \geq 3$ and 0.97 (0.93–1) for $F = 4$. An interesting study, performed by Casterà et al. (15), evaluated the performance of TE in patients suffering from chronic HCV infection, in comparison with and combined with currently available biochemical markers, in particular with the FibroTest, BioPredictive (a six parameters scoring system that allow the quantification of liver fibrosis) (18) and the aspartate transaminase to platelets ratio index (APRI – a index particularly related to the stage of fibrosis) (19). The LB examinations were performed on the patients on the same reference day. The TE and FibroTest diagnostic values were very similar and only better than the APRI score. The detected cut-offs were similar to those described by Ziol, with 7.2 kPa for $F \geq 2$ and 12.5 kPa for cirrhosis. The best performance was obtained by combining TE and FibroTest, with areas under ROC curve of 0.88 (0.82–0.92) for $F \geq 2$, 0.95 for $F \geq 3$ (0.91–0.97) and 0.95 for $F = 4$ (0.91–0.97) (Table 1). An Italian study (20) compared LB, biochemical markers of fibrosis and TE in 40 HCV-infected patients with normal

Table 1 Analysis of TE cut-off for the diagnosis of METAVIR fibrosis score

Lead author	Ziol	Castera	Foucher
F ≥ 2			
AUROC	0.79	0.83	0.80
Optimal cut-off (kPa)	8.8	7.1	7.2
Sensitivity (%)	56	67	64
Specificity (%)	91	89	85
PPV (%)	88	95	90
NPV (%)	56	48	52
F ≥ 3			
AUROC	0.91	0.90	0.90
Optimal cut-off (kPa)	9.6	9.5	12.5
Sensitivity (%)	86	73	65
Specificity (%)	85	91	95
PPV (%)	71	87	90
NPV (%)	93	81	80
F = 4			
AUROC	0.97	0.91	0.96
Optimal cut-off (kPa)	14.6	12.5	17.6
Sensitivity (%)	86	87	77
Specificity (%)	96	91	97
PPV (%)	78	77	91
NPV (%)	97	95	92

AUROC, area under receiver operative curve; PPV, positive predictive value; NPV, negative predictive value.

transaminases. The conclusion of this study was that among HCV carriers with normal transaminases TE is higher than that of FibroTest as regards the noninvasive detection of fibrosis. Moreover, the TE is a monitoring method of the fibrosis progression in HCV-infected patients subjected to antiviral treatments. Preliminary data relevant to a group of 211 patients treated by pegylated interferon and ribavirin (21) show an important reduction in the elastography values testifying the antifibrotic action of the therapy as well as the correlation with the sustained virological response. Recently, Carrión et al. (22) evaluated the prospective diagnostic accuracy of TE to assess the severity of hepatitis C recurrence after liver transplantation in 124 patients. In this cohort 169 liver biopsies and 129 hepatic haemodynamic studies with determination of hepatic venous pressure gradient (HVPG) were performed. At the same time patients underwent a liver stiffness measurement. Liver fibrosis turned out to be mild (F0–F1) in 96 patients and significant (F2–F4) in 73. HVPG turned out to be normal (< 6 mm Hg) in 69 patients and elevated (≥6 mm Hg) in 60 (46%). Using a liver stiffness cut-off value of 8.5 kPa for the diagnosis of fibrosis F ≥ 2 sensitivity, specificity, negative predictive value and positive predictive value were 90%, 81%, 79% and 92% respectively. Areas under ROC curve for the diagnosis of fibrosis ≥ F2, ≥ F3 and F4 were 0.90, 0.93 and 0.98 respectively. There was a close direct correlation between liver stiffness and HVPG and the area under ROC curve for diagnosis of portal hypertension was 0.93. Finally, none of patients with liver stiffness below the cut-off value showed either bridging fibrosis (F3), cirrhosis (F4) or significant portal hypertension (HVPG ≥ 10 mm Hg). The authors concluded that TE is an extremely valuable tool in assessing the severity of HCV recurrence after LT and in reducing the need for follow-up LBs. Recently, a French group has compared the additional value of elastography with physicians assessment of fibrosis in 142 HCV-infected patients (23). Four physicians, two junior residents and two senior hepatologists, independently estimated the stage of fibrosis according to the METAVIR classification, using clinical, epidemiological and biological data. Later on they were informed of elastographic values and could modify their first evaluation if necessary. The two successive evaluations were compared with the histological fibrosis score. The authors concluded that providing elastographic values to physicians results in a better estimation of liver fibrosis and a more accurate diagnosis of cirrhosis. Moreover, it allows physicians with limited experience to predict liver fibrosis as well as experienced hepatologists. Finally Coco et al. (16) measured liver stiffness by TE in 228 consecutive patients with chronic viral hepatitis (HCV and HBV), with or without cirrhosis, to study its correlations with serum transaminases, fibrosis stage and surrogate noninvasive markers of fibrosis. The authors reported that TE showed higher diagnostic accuracy than other noninvasive surrogate markers of fibrosis in chronic viral hepatitis patients and may reduce the number of LBs for clinical decision-making, provided that its relationship with major changes of biochemical activity is taken into account.

Elastographic evaluation of HCV cirrhosis

Foucher et al. (24) evaluated the accuracy of TE for the detection of cirrhosis in 711 patients with liver diseases in various aetiologies, 398 with HCV chronic infection. The results of this study redefined the elastometric cut-off for the diagnosis of hepatic fibrosis stage, and in particular for the diagnosis of cirrhosis (Table 1). In the same study the authors identified the cut-off directly correlated with the presence of complications in cirrhosis, in particular: oesophageal varices stage 2/3 (27.5 kPa), cirrhosis Child-Pugh B/C (37.5 kPa), past history of ascites (49.1 kPa),

hepatocellular carcinoma (53.7 kPa) and variceal bleeding (62.7 kPa). This data and in particular the ability to detect oesophageal varices in cirrhotic patients was subsequently confirmed by Kazemi et al. (25). One-hundred and forty patients with histologically proven cirrhosis underwent both oesophageal endoscopy and TE. With cut-off under 20 kPa, the authors confirmed the absence of grade 2/3 oesophageal varices and gastric fundal varices, with a negative predictive value of 99%. The authors speculated about the possibility to avoid gastro-oesophageal endoscopy in 50% of their patients by the use of this cut-off value. In a prospective study, de Ledinghen et al. (26) evaluated liver stiffness measurement using TE in 72 HIV–HCV co-infected patients comparing it with other noninvasive methods. In this study the area under the ROC curve was 0.72 (0.60–0.84) for $F \geq 2$ and 0.97 (0.94–1.0) for cirrhosis. For the diagnosis of cirrhosis the optimal cut-off value of liver stiffness was 11.8 kPa. Moreover, this study reported the superiority of TE relative to aspartate aminotransferase/alanine aminotransferase ratio and to APRI score for noninvasive diagnosis of virus-related hepatic fibrosis. The authors concluded that liver stiffness measurement is a promising noninvasive method for the assessment of fibrosis in HIV-infected patients with chronic HCV infection. Recently, Ganne-Carrié et al. (27) evaluated the TE accuracy in detecting cirrhosis in 1257 patients with chronic liver diseases of various aetiologies, enrolled in a prospective multi-centre study. Two-hundred and fifty patients were excluded for unsuitable biopsy specimens and unreliable TE measurement. Because the study overlapped a previous one (14), the analysis was performed on 775 new patients including 339 with HCV chronic infection alone or with alcohol abuse, and 120 with cirrhosis. The ROC curve analysis was used to assess the diagnostic accuracy. The area under ROC curve was 0.95 (0.93–0.96) in the whole population. The optimal cut-off for the diagnosis of cirrhosis was 14.6 kPa (positive and negative predictive values, 74% and 96%) with discrepancies among the aetiological groups. This data, compared with others studies, suggests that the cut-off values for the diagnosis of cirrhosis is specific for each aetiological group. It can be assumed that this difference is a consequence of discrepancies in fibrosis lesions and inflammation degree in different diseases.

Factors associated with the success rate of TE have been recently evaluated in a prospective study (11). Authors have compared liver stiffness measurements with fibrosis stages assessed on LB in 935 patients with HCV chronic infection and showed operator experience, body mass index and patients' age independently influenced the success rates of TE measurements. For patients with F0–F1, F2, F3 and F4 fibrosis, median liver stiffness measurement was 5.4, 6.8, 10.3 and 17.6 kPa respectively. These results obtained in a large sample also confirm that TE is a valuable method for the evaluation of cirrhosis in HCV patients with a performance in the same range as previously reported (14,15). In according with this data, Fraquelli et al. (12) reported that intra-observer agreement is almost absolute after a 1 month of daily practice only, indicating that performance can be maximised after a short initial training period. The study by Kettaneh et al. (11) also evaluated relationship between the number of valid measure for each patient and TE accuracy for the diagnosis of cirrhosis. By comparing the diagnostic accuracy of the 10 shot examinations (the minimum recommended) (9), with that of five and three shot examinations, the authors suggest that five valid shots could be sufficient to obtain an accurate TE examination.

Conclusions

Transient elastography is a rapid and noninvasive marker of fibrosis assessment offering specialists a new way to supervise the patients suffering from chronic liver diseases and in particular for HCV infection (10,11). TE provides a quantitative operator-independent measurement of liver stiffness. The best known contributor to liver stiffness is the amount of fibrosis; however, literature suggest that inflammation process, interstitial fluid and even micro-vascular conditions can have an impact on the stiffness measurement obtained by TE. Thus, this method has the potential to provide much more information than just an assessment of fibrosis; it rests on specialists to place the elastographic results in perspective with the rest of their clinical findings so as to establish a view of the clinical case at hand. In clinical practice high TE values may be accurate in assessing the severity of liver disease, to suspect the presence of complications and, consequently, in providing a follow-up programme. In particular, TE allows to predict the presence of large oesophageal varices in patients with cirrhosis and may help to select patients for endoscopic screening (24). Once validated for assessment of degree of disease in chronic HCV infection, the TE effectiveness will have to be confirmed in the other chronic liver diseases, where specific consensus cut-off is to be developed. With an aim at the follow-up of liver fibrosis in a treated or non-treated patient, the place of LB is questionable. If preliminary data present in literature are confirmed, TE would be a technique adapted to monitoring patients suffering from HCV chronic

infection and subjected to interferon treatment, able to modify the evolution of the fibrosis.

In conclusion, TE is a technique adapted to monitor the progression of liver disease. However, TE results must be interpreted according to the background of clinical examination, laboratory, sonography, endoscopic results and liver histology.

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