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EDITORIAL

Transient elastography for the assessment of chronic liver disease: Ready for the clinic?

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Abstract

Transient elastography is a recently developed non-invasive technique for the assessment of hepatic fibrosis. The technique has been subject to rigorous evaluation in a number of studies in patients with chronic liver disease of varying aetiology. Transient elastography has been compared with histological assessment of percutaneous liver biopsy, with high sensitivity and specificity for the diagnosis of cirrhosis, and has also been used to assess pre-cirrhotic disease. However, the cut-off values between different histological stages vary substantially in different studies, patient groups and aetiology of liver disease. More recent studies have examined the possible place of transient elastography in clinical practice, including risk stratification for the development of complications of cirrhosis. This review describes the technique of transient elastography and discusses the interpretation of recent studies, emphasizing its applicability in the clinical setting.

Key words: FibroScan; Transient elastography; Liver stiffness measurement; Hepatic fibrosis; Hepatitis

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INTRODUCTION

The management and prognosis of chronic liver disease is strongly influenced by its severity. While percutaneous liver biopsy remains the gold standard, there is increasing awareness, not only of the associated morbidity and mortality of the procedure, but also its diagnostic limitations. There is considerable sampling variability, and inter- and intra-observer variation in the assessment of liver pathology. Antifibrotic therapies are in development, but it has been stated that "the lack of robust markers of fibrosis represents the single greatest factor limiting both the validation of progression or regression of fibrosis and the testing of antifibrotic therapies"[1].

A number of approaches to non-invasive assessment of chronic liver disease have been developed. Serum markers, and serum panel markers for the assessment of chronic liver disease, such as the APRI (AST to platelet ratio index) score, Enhanced (European) Liver Fibrosis (ELF™) test and FibroTest, have been proposed, and are the subject of several comprehensive reviews[2-4]. Investigations based on imaging modalities, including ultrasound and magnetic resonance, are liver-specific and provide structural information related to the liver[5]. Microbubble contrast-enhanced ultrasound to obtain hepatic vein transit times (HVTT) and phosphorus-31 magnetic resonance spectroscopy (^{31}P MRS) have been shown to delineate cirrhotic and pre-cirrhotic disease stages, but require considerable operator skill and access to the relevant technology[6-10]. Other MR techniques, such as diffusion-weighted imaging (DWI) and ultrashort echotime (UTE) have shown promise, but require further development[11,12]. Moreover, these techniques require assessment in larger subject groups in the setting of multi-centre trials.

Liver stiffness measurement using transient elastography (TE) (FibroScan®) is a recently developed technique designed for the assessment of liver fibrosis, and has been extensively evaluated in several recent studies. The aim of this article is to review the current data on the use of transient elastography in clinical practice and to make recommendations for future research. A Medline search using the terms "FibroScan" and "transient elastography" was conducted. The proceedings of the 41st annual meeting of the European Association for the Study of the Liver 2006, and the 57th annual meeting of the American Association for the Study of Liver Diseases 2006 were also searched for relevant articles.

THE BASIS OF TRANSIENT ELASTOGRAPHY

Transient elastography allows liver stiffness measurement (LSM) which enables the assessment of liver disease severity, using a 1-dimensional ultrasound transducer and receiver mounted on the same axis as a vibrator, producing a low-frequency pulse or shear wave. When the probe tip is placed perpendicularly against the skin between the ribs overlying the liver and triggered, the rate of progression of the shear wave is measured.

The speed of propagation depends on the elasticity or stiffness of the tissue under examination and is measured by a series of ultrasonic pulses, which detect the transient local deformations in the liver tissue as the shear wave progresses. The elasticity of the liver is derived from the velocity of the wave approximating to the Young's modulus, E, according to the equation: $E = 3\rho V_s^2$ where V_s is the shear velocity and ρ is the mass density, assumed to be close to that of water. The deformation of tissue is plotted as a function of time and depth to create a two-dimensional "elastogram". The slope of the elastogram represents the speed of propagation and thus the liver stiffness, expressed in kPa[13].

This technique is simple to learn, can be performed quickly by a single operator, and provides an objective measure of liver stiffness. TE has been employed in a number of clinical paradigms over the last few years, however, there is at present no consensus on its indications for use, interpretation and applicability.

ANALYSIS AND EVALUATION

Most studies carried out to evaluate the performance of transient elastography compare LSM to the histological assessment of liver biopsy. Of these, the METAVIR scoring system which is widely used in clinical practice has been employed in the majority of studies[14]. Fibrosis is staged semi-quantitatively on a five-point scale from F0 to F4 (F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis and few septa; F3 numerous septa without cirrhosis; F4, cirrhosis). Divisions of clinical significance are considered to be between F1 and F2 (from minimal to significant fibrosis) and between F3 and F4 (from fibrosis to cirrhosis). The data obtained is commonly represented by boxplots with liver stiffness (or $\log_{10}$ liver stiffness) on the y axis and fibrosis stage on the x axis, representing the median, interquartile range and range of values for individuals at each fibrosis stage. Despite an apparently high diagnostic accuracy, there is substantial overlap between groups, especially in the pre-cirrhotic stage of liver disease. This has clinical implications since for a given liver stiffness measurement, the patient's true fibrosis score may vary from F0-1 to F4[15].

A major criticism of liver biopsy and an important stimulus to the development of non-invasive techniques is the small portion of liver that is assessed. The specimen obtained by standard liver biopsy techniques represents just 1/50 000 of the liver, and typically only 16% of such biopsies exceed the optimal length of 25 mm required for adequate histological assessment[16]. This results in significant sampling variability since hepatic fibrosis, inflammation and steatosis may have a patchy spatial distribution within the liver. Added to this drawback is the presence of inter- and intra- observer variability in histological assessment, making this "gold-standard" considerably flawed. Thus, non-invasive measures such as TE are judged by liver biopsy which may be a flawed standard. Clearly, the results obtained should be regarded as a probability of correctly predicting liver fibrosis and interpreted in the context of clinical, epidemiological and biochemical data, and moreover should be correlated prospectively with robust clinical outcome measures.

ASSESSMENT OF DIAGNOSTIC ACCURACY

While the sensitivity, specificity, positive and negative predictive values describe the performance of a test with respect to a gold-standard, diagnostic accuracy provides a measure of the overall performance of a test. Diagnostic accuracy of transient elastography with respect to histology has been measured in clinical studies using the area under the receiver operator characteristic (ROC) curve, a convenient non-parametric method for the assessment of diagnostic tests, compared to a gold-standard. The sensitivity is plotted against 1- specificity for all possible cut-off values between two states. For example, this could be expressed as: positive or negative; cirrhosis or no cirrhosis; insignificant or significant fibrosis. A measure of diagnostic accuracy of the test may be derived, whereby an area near 1 represents high diagnostic accuracy. ROCs may be used to select cut-off values appropriate to different scenarios. Cut-off values may then be selected for a given situation according to the required sensitivity or specificity of a given value to distinguish the two states. This allows cut-off values to be chosen to answer clinically relevant questions. For example, to rule out cirrhosis effectively in a group of patients, a cut-off value with a specificity of 95% may be used, indicating that there is a 95% probability that patients below the cut-off value will not have cirrhosis. Alternatively, an optimum cut-off may be calculated, where the cut-off is chosen at the point where the sum of sensitivity and specificity is maximal, although this is affected by the shape of the ROC curve and therefore may vary between studies. A more inclusive measure would be obtained by using a cut-off associated with high sensitivity but lower specificity.

The largest study published to date demonstrates that different cut-off values for the diagnosis of cirrhosis exist, depending on the sensitivity and specificity required for the decision and for different aetiologies, such as chronic hepatitis B, chronic hepatitis C and alcohol-related and non-alcoholic related fatty liver disease (Table 1)[17].

TRANSIENT ELASTOGRAPHY FOR STAGING OF HEPATIC FIBROSIS

Initial clinical studies using TE investigated the ability of

Table 1 Liver stiffness cut-off values for the diagnosis of cirrhosis according to the primary cause of liver disease

	Optimum cutoff (kPa)		
	Hepatitis C (*n* = 298)	Hepatitis B (*n* = 122)	Alcohol or NASH (*n* = 122)
Sensitivity 95%	10.0	6.0	13.2
Max. sum of sensitivity and specificity	10.4	10.3	21.5
Best diagnostic accuracy	20.2	16.9	21.5
Specificity 95%	14.1	14.3	27.7

NASH: Non-alcoholic steatohepatitis. Data obtained from Ganne-Carrie *et al* 2006[17].

the technique to assess hepatic fibrosis when compared to the gold standard of liver biopsy. This was assessed by Sandrin and colleagues in a "proof-of-principle" study. They demonstrated a graduated increase in liver stiffness with increasing hepatic fibrosis[13]. Chronic hepatitis C was chosen as the paradigm for many studies as the patients are numerous and the natural history of the disease and histological classification systems have been well described[14,18]. Other workers have investigated the ability of TE to assess fibrosis compared to liver biopsy in several disease paradigms, as summarised in Table 2[13,15,17,19-25].

Hepatic fibrosis is a complex and multistep process. Therefore, a precise description of disease severity may require assessment of more than one aspect of the disorder. TE measures liver stiffness which is thought to be due largely to the extent of fibrosis. Indeed digital image analysis demonstrates a correlation between the fibrotic area and liver stiffness[26]. Yet, the extent of fibrosis does not provide the complete picture. Histological scoring systems are not linear and in addition to the extent, they describe the pattern of deposition of fibrous tissue[18,14]. The effect of collagen cross-linkage on liver stiffness, associated with more severe disease, has not been clearly established. More recently, a strong relationship between liver stiffness and the hepatic venous pressure gradient (HVPG) has been described, demonstrating an association with portal hypertension[27]. The relative contribution of fibrosis, inflammation and haemodynamic changes have yet to be determined.

A recent well-conducted study by Fraquelli and colleagues looked specifically at the reproducibility of LSM in 195 patients with liver disease of mixed aetiology (predominantly HCV)[24]. The results obtained by two different operators working under highly regulated conditions, showed a very high degree of inter-observer agreement, with an intraclass correlation coefficient (ICC) of 0.98, representing an estimated 98% of variability due to patient characteristics, as opposed to observer variability. This agreement was substantially reduced when groups such overweight patients, those with histological or ultrasound evidence of hepatic steatosis and especially those with mild disease (ICC 0.6 for METAVIR F0-1 *vs* 0.99 for F $\geqslant$ 2) were assessed. There were stringent inclusion criteria such as inclusion of only those patients in whom a success rate of > 65% was achieved and where the interquartile range of the readings was less than 30% of the median. Additionally, 76% of liver biopsy specimens exceeded 20 mm in length, thus minimising sampling error. Despite the high reproducibility of LSM, there was substantial overlap in the findings between adjacent stages of hepatic fibrosis, which the authors acknowledged would limit the diagnostic accuracy of TE, particularly in intermediate fibrosis stages.

Disease activity or necro-inflammation are not directly assessed by TE, although LSM has been shown to increase with increasing necroinflammatory scores at histology[24], and in biochemically-assessed flares of hepatitis and cirrhosis[28]. Steatosis is a cause as well as a consequence of chronic liver disease[29], and its effect on liver stiffness is believed to be minimal based on multivariate analyses in studies investigating other endpoints[15,30]. However, studies assessing the severity of liver stiffness stratified by the degree of steatosis are awaited. The development of serum panel markers of hepatic fibrosis demonstrates recognition of the fact that multiple diagnostic measures are required. Castera and colleagues compared TE with FibroTest, an indirect serum panel marker, and the AST to platelet ratio index (APRI) in a cohort of patients with chronic hepatitis C, and found equivalent results with these techniques, but noted that a combination of TE and the serum panel marker provided the greatest diagnostic accuracy[19]. On this basis, an algorithm was proposed whereby liver biopsy can be avoided in most patients with chronic hepatitis C when the tests are in agreement[19]. Other studies have demonstrated a similar diagnostic accuracy of TE in the context of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) coinfected patients[23], and also in the presence of biliary fibrosis in patients with primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC)[20,23].

CIRRHOSIS AND ITS COMPLICATIONS

In view of the wide range of LSM for any single fibrosis stage, attention has turned to the use of FibroScan in the diagnosis of cirrhosis and of its complications such as varices, risk of variceal bleeding, hepatocellular carcinoma and ascites. Foucher and colleagues examined prospectively a cohort of patients with liver disease of varying aetiology[25]. In addition to establishing the cut-off values for fibrosis of varying severity as assessed by liver biopsy, they calculated the cut-off values below which there was a 90% chance that complications such as varices (stage 2/3) (27.5 kPa), Child-Pugh score of B/C (37.5 kPa), ascites (49.1 kPa), and oesophageal bleeding (62.7 kPa) were absent. Although the number of subjects with each complication was small (between 14 and 42 cases), these cut-off values may serve to identify patients with cirrhosis at risk of such complications. However, history of ascites, hepatocellular carcinoma, and variceal bleeding may be readily obtained by direct questioning of the patient, therefore for these observations to be clinically useful, they need to be borne out in prospective studies on the development of these complications over time. Kazemi and colleagues correlated endoscopic evidence of oesophageal varices with LSM in a cohort of patients with

Table 2 Results of studies in which liver stiffness was compared with histological fibrosis stage (METAVIR system) to establish diagnostic accuracy and cut-off values

Author, yr	Patient group	Number of subjects	Cut-off for F ⩾ 2 (kPa)	AUROC F ⩾ 2	Cut-off for F = 4 (kPa)	AUROC F = 4
Fraquelli M *et al* 2007[24]	Mixed (HCV)	195 (155)	7.9 (72%; 84%)	0.86	11.9 (91%; 89%)	0.90
Ganne-Carrie N *et al* 2006[17]	Mixed (HCV)	1007 (298)			14.6 (79%; 95%)	0.92
De Ledinghen V *et al* 2006[23]	HCV/HIV co-infected	72	4.5 (93%; 17%)	0.72	11.8 (100%; 93%)	0.97
Gomez-Dominguez E *et al* 2006[22]	Mixed (HCV)	94 (62)	4 (94%; 33%)	0.74	16 (89%; 96%)	0.94
Carrion J *et al* 2006[21]	HCV post transplant	169	8.5 (90%; 81%)	0.90	12.5 (100%; 87%)	0.98
Corpechot C *et al* 2006[20]	PBC/PSC	101	7.3 (84%; 87%)	0.92	17.3 (93%; 95%)	0.96
Foucher J *et al* 2006[25]	Mixed	354	7.2 (64%; 85%)	0.80	17.6 (77%; 97%)	0.96
Castera L *et al* 2005[31]	HCV	183	7.1 (67%; 89%)	0.83	12.5 (87%; 91%)	0.95
Ziol M *et al* 2005[15]	HCV	251	8.8 (56%; 91%)	0.79	14.6 (86%; 96%)	0.97
Sandrin *et al* 2003[13]	HCV	106		0.88		0.99

Cut-off values were those proposed by the authors. If more than one cut-off value was available, the value set for optimum diagnostic accuracy (i.e. cut-off at which sensitivity (se) + specificity (sp) is maximal) was used. Cut-off values are followed by the relevant sensitivity and specificity in parenthesis. HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; PSC: Primary sclerosing cholangitis; PBC: Primary biliary cirrhosis.

compensated cirrhosis, and observed that a cut-off value of 19 kPa predicted varices (stage Ⅱ/Ⅲ) with a sensitivity of 91% and specificity of 60%[31]. These findings suggest that endoscopic surveillance can be avoided in up to 60% patients with cirrhosis.

TOWARDS THE CLINIC

Ganne-Carrie and coworkers have published the largest series to date, but have concentrated on separation of cirrhotic from precirrhotic disease[17]. These authors highlighted the fact that the cut-off values vary on the basis of the aetiology of liver disease as well as the level of sensitivity and specificity required for the issue under question (Table 1). There were substantial differences in the cut-off values for the prediction of cirrhosis with 95% specificity depending on the number of patients studied (775 *vs* 1007). It remains to be seen whether the cut-off values vary depending on the population of interest, for example in affluent societies with high level of co-existent type 2 diabetes and hepatic steatosis, compared to a group with few risk factors for steatosis.

Of particular interest is the question whether liver stiffness measurement affects clinical decision making. For example, a non-invasive technique, such as TE, is particularly desirable in patients with bleeding disorders, such as haemophilia. Two studies have addressed this issue. Masaki and colleagues correlated LSM with ultrasound assessment of liver disease and several serum markers in haemophiliacs coinfected with HCV and HIV, although the findings were not linked to a clear standard or to clinical outcome measures and decisions[32]. Posthouwer and colleagues studied a cohort of patients with haemophilia and chronic hepatitis C in whom percutaneous liver biopsy was contraindicated[33]. Cut-off values from a previous study were applied[19] and validated in a separate cohort of patients without a bleeding disorder. This study demonstrated the pragmatic use of TE in a specific scenario with acknowledgement that there will be inaccurate assessment in a proportion of patients. In such a scenario, a false positive test may result in a patient with mild disease receiving antiviral therapy while a patient with a false negative test, may have severe disease and not receive treatment. It can be argued that the latter group may have a detrimental outcome, and therefore a cut-off with a higher sensitivity is indicated.

An important indication for non-invasive staging of hepatitis C-related liver disease is to determine whether antiviral treatment is appropriate in a particular patient[15]. However, on the basis of recent studies in patients with mild hepatitis C, current UK treatment guidelines suggest that treatment is both clinically effective and cost-effective in histologically mild, moderate and severe stages of pre-cirrhotic disease[34-36]. Increasingly, patients with functionally-compensated cirrhosis are being treated, although the likelihood of a good response to treatment is smaller in this group. Since treatment is not contraindicated in any histological group of patients with hepatitis C, the role of such non-invasive technologies should be questioned. It is possible that the evaluation of liver stiffness may provide risk assessment on the basis of which further investigations should be planned. Such a scheme may allow a period of "watchful waiting" prior to a decision on starting treatment, in addition to providing reassurance to patients with mild disease. Another area of interest is the patient's response to treatment. Preliminary data indicates that LS decreases in patients with hepatitis C after treatment with pegylated interferon and ribavirin and that the decrease is greater in virologic responders compared to non-responders[37]. This alteration may reflect biochemical changes associated with disease activity, as opposed to changes in fibrosis *per se*, and the long term outcome data in a large cohort of patients is awaited.

Nahon and colleagues addressed the issue of how LSM may affect clinical assessment by inviting four physicians to predict the fibrosis stage on the basis of routine history, physical examination and biochemical tests[38]. Liver stiffness measurement was performed at the time of liver biopsy. The physicians were allowed to modify their estimate of disease severity in the light of the LSM findings, which were then compared with the biopsy results. LSM did not significantly enhance the physicians' prediction of pre-cirrhotic disease staging compared to the assessment based on routine investigations. In the

prediction of cirrhosis, the addition of LSM improved the diagnostic accuracy by about 10% in results obtained by 3 out of the 4 physicians.

The utility of TE in routine clinical assessment of precirrhotic disease appears questionable in the light of data currently available. Routine abdominal ultrasound is carried out in nearly all patients with chronic liver disease to assess structural abnormalities, and to look for cholestasis, portal hypertension and hepatocellular carcinoma. The presence of findings such as increased heterogeneity, irregular liver outline or nodularity, caudate lobe hypertrophy, increased spleen size, and portal vein Doppler blood flow measurement all provide evidence of cirrhosis, with high specificity, but relatively low sensitivity[39,40]. It is possible that routine ultrasound enhances the physician' s assessment of whether a patient has cirrhosis, while in addition providing the additional information described above. However, it should be noted that in the study by Nahon and colleagues, of the 15 patients misclassified as cirrhosis after LSM by the senior physicians, 3 had features of cirrhosis on ultrasound or endoscopy[38]. It is not clear how many of the patients correctly classified on the basis of LSM would have also been correctly classified had routine ultrasound information been provided. Therefore, before LSM is recommended for routine clinical use, the existing technologies should be compared by employing analogous methods of analysis.

CONCLUSION

Assessment of TE using FibroScan is a novel technique that has been evaluated in a number of well-conducted studies. It is a safe, acceptable and quick technique that provides an objective and reproducible measure of liver stiffness. LSM correlates with histological fibrosis score, but the cut-off values vary depending on the study referred to, the aetiology of the disease and the sensitivity and specificity required. LSM provides high diagnostic accuracy for the detection of cirrhosis, making it a potentially useful tool for population-based screening for cirrhosis in areas of high prevalence. However, the delineation of pre-cirrhotic stages is less clear, although LSM compares well with serological markers of fibrosis such as the APRI score and FibroTest[19]. LSM has a number of drawbacks which include that is technically challenging in obese individuals, where it is associated with reduced success rate; it is not possible to perform in the presence of significant ascites; and the effect of marked steatosis has not been addressed.

Recent studies have begun to address the likely place of LSM in routine clinical practice and the impact it may have on physicians' assessment of disease severity. However, several important questions remain to be resolved including: what are the relative contributions of fibrosis and haemodynamic alterations on LSM? How does steatosis affect LSM? Which cut-off values should be used for which indication? Does LSM substantially add to the information already obtained by routine clinical assessment, abdominal ultrasound and simple blood tests such as the APRI score? Is LSM sufficiently sensitive to detect changes in fibrosis over the long term; in terms of both disease progression and response to treatment?

While such information is awaited, LSM is being performed increasingly worldwide as a result of increased awareness of the technique. The following recommendations are made for consideration when employing the technique: (1) As different cut-off values exist for different diseases, the diagnosis should always be obtained prior to interpretation of the LSM. (2) The clinical question should be defined in order that a cut-off value is used incorporating the appropriate sensitivity and specificity. (3) Criteria in terms of success rates and minimum number of readings should be defined so that assumptions are not made on the basis of inadequate data. (4) Comparison should be made with liver biopsy, if available, in order to provide continual validation. (5) The process of continuous audit should be instituted, with particular emphasis on how such measurements influence decision-making.

THE FUTURE OF IMAGING BIOMARKERS

Fibrosis and fibrogenesis is a complex multistep process. It would be surprising if a single biomarker was able to provide complete evaluation of the disease. FibroScan is an innovative and user-friendly technology but, despite strong academic and commercial promotion, its limitations have been described in a several well-conducted studies. Assessment of precirrhotic disease and the longitudinal assessment of change in fibrosis have not been fully evaluated. A comprehensive, non-invasive assessment of chronic liver disease will be very helpful for baseline assessment of disease and to evaluate the impact of new antifibrotic therapies. Serum panel markers and imaging techniques including ultrasound and magnetic resonance modalities need to be investigated longitudinally in a number of disease states in order to develop and identify the most effective combination of tests, of which TE with FibroScan may be one. The challenge is to develop and validate such a protocol, and to correlate the results with clinically meaningful outcome measures.

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