Reproducibility and accuracy of Point Share Wave Elastography in the assessment of liver stiffness in patients with chronic liver disease

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ABSTRACT

**Purpose:** To evaluate the reproducibility and diagnostic accuracy of "real time" Shear Wave Elastography in the measurement of liver stiffness in patients with chronic viral hepatitis B and C and in a group of healthy volunteers.

**Materials and methods:** A consecutive series of patients with chronic viral hepatitis B and C and a group of healthy volunteers were evaluated. Patients with chronic liver disease underwent liver biopsy. The degree of liver fibrosis was assessed according to the METAVIR "score system". Measurements of liver stiffness were performed by an experienced radiologist (observer 1) and two less experienced radiologists (observers 2 and 3). Measurements were made by each observer in least three different points of liver parenchyma. In each patient, were acquired 12 consecutive measurements for a total time acquisition of about 5-10 minutes per patient by using iU22 ultrasond system (Philips Medical Systems) with a dedicated convex probe. The degree of liver stiffness measured in kPa was recorded and displayed automatically at the end of each measurement. The results of the "real time" Shear Wave Elastography evaluation, corresponding to the average of 12 measurements, were displayed at the end of each measuremet. They evaluated 57 patients with chronic liver disease and 37 healthy volunteers (50 males and 44 females, aged between 19 and 80 years). The average value of the measurements were of 9.7 kPa in patients with chronic liver disease and 5.5 kPa in the group of healthy volunteers.
**Results:** The "real time" Shear Wave Elastography measurements showed a good correlation with the results of the biopsy relatively to the stage of fibrosis (p <0.001). An excellent reproducibility was observed in measurements between the three observers (ICC, 0.85; 95% confidence interval: 0.70 to 0.94).

**Conclusion:** The "real time" Shear Wave Elastosography showed to be a reproducible method and accurate in measuring the stiffness of the liver parenchyma in patients with chronic liver disease and in the group of healthy volunteers. Healthy volunteers showed significantly lower values with respect to patients with chronic liver disease.
INTRODUCTION

Patients with chronic viral hepatitis B and C are at increased risk of cirrhosis. Assessment of fibrosis has important prognostic implications that guide clinical therapy (1,2). The prognosis and management of chronic viral hepatitis depend on the extent and progression of liver fibrosis, which constitute the most important predictor of disease outcome and influence the indication for antiviral treatment (3).

Though liver biopsy is still the reference standard for diagnosis and grading of fibrosis, it is invasive and carries risk of complications.

In the last decade, methods to noninvasively quantify liver fibrosis have been developed. The first available method was Transient Elastography (4). Several studies have demonstrated a high accuracy of Transient Elastography in identifying significant fibrosis ($F > 2$) and cirrhosis ($F = 4$) in patients with chronic viral hepatitis (5-9).

The recent guidelines for the management of viral hepatitis infection from the European Association for the Study of the Liver allow the use of Transient Elastography, instead of liver biopsy, in patients with chronic viral hepatitis for assessing liver disease severity prior to therapy at a safe level of predictability (10). Transient Elastography has been approved by the French National Health Authority for the evaluation of fibrosis in treatment-naïve
patients with chronic viral hepatitis and no comorbidities (11).

Shear Wave Elastography techniques have been implemented in conventional real-time ultrasound systems, and several studies have shown their accuracy in the assessment of liver fibrosis (12-16). Compared with Transient Elastography, these techniques have the advantage of B-mode image guidance; thus, they can allow the user to choose the best acoustic window for correctly performing an examination in real time.

Magnetic Resonance (MR) Elastography is based on the use of Shear Wave Elastography induced in tissues by external surface vibrators. MR Elastography also showed promising results for quantification of liver fibrosis with high accuracy (17-19). However, MR Elastography has some limitations. It is imprecise for detection of early levels of fibrosis and for quantitation of intermediate levels of fibrosis. There is overlap between adjacent stages of fibrosis, especially in the precirrhotic stage of liver disease. The difference is small in grade F0–F2 fibrosis, but it is larger in grades F3 and F4 (19,20). The acquisition time for MR Elastography is long (10–15 minutes), and therefore it is limited to static organs and precludes freehand applicability (21). Technically, the delivery of Shear Wave Elastography by MR Elastography into the abdomen may be imperfect, and it may lead to error in interpretation and calculation (20).

Shear Wave Elastography allows absolute quantification of tissue stiffness in terms of pressure unit of kilopascals versus a semiquantitative estimate that corresponds to relative tissue strain (22).
The aim of this study was to estimate the validity of Shear Wave Elastography by evaluating the reproducibility and the accuracy of this method in the measurement of liver stiffness in patients with chronic viral hepatitis B and C and in a group of healthy volunteers.
MATERIALS AND METHODS

Between January 2014 and March 2015, 94 consecutive patients (50 males and 44 females, aged between 19 and 80 years) were included in the study. Fifty-seven patients were suffering from chronic viral hepatitis histologically proven (B=22 and C=35), and the remaining 37 patients were healthy volunteers.

Patients with chronic hepatitis B or C virus induced did not receive antiviral therapy or antifibrotic. The assessment excluded patients with hepatocellular carcinoma with hepatic insufficiency or with ascites. Patients whose elastosonographic measurements were not satisfactory or patients who refused to undergo liver biopsy were also excluded. The patients underwent liver biopsy within 12 months of elastosonographic evaluation. A recent study has shown that a delay between the liver biopsy and the elastosonographic evaluation of about 15 months is acceptable because the expected changes in the level of the liver parenchyma are minimal (23).

The group of healthy volunteers did not present a significant past medical history, including diabetes or hypertension. They did not show a high intake of alcohol (defined as <30 g of alcohol per day for men and <20 g for women), presented negative serological tests for hepatitis B and hepatitis C and did not present biochemical or ultrasound findings typical for liver disease. They did not make chronic use of drugs or substance abuse. Healthy volunteers whose elastosonographic measurements were unsatisfactory were
excluded from the evaluation.

None of the observers was made aware of the clinical data of patients and of their “real time” Shaer Wave Elastography results.

Elastosonography measurements were made using the iU22 ultrasound system (Philips Medical System) with a dedicated convex probe. The elastosonographic evaluation was performed at the end of each ultrasound and ultrasound color Doppler examination. In all cases, the measurements were carried out at the level of the liver parenchyma of employing a right intercostal approach, since a subcostal approach is not always feasible. In addition, the intercostal approach results in less external compression on the liver parenchyma (4). Patients were instructed to maintain a steady breathing that was made at the time of measurement block to avoid breathing artifacts. The measurements were carried out at a depth between 20 and 50 mm, identifying an area not contiguous to the main intrahepatic vascular structures. The evaluation included at least 12 correct measurements per patient with a total acquisition time of about 5-10 minutes. The degree of liver stiffness measured in kPa was recorded and displayed automatically after each correct measurement as well as the evaluation results corresponding to the average of 12 measurement (Fig. 1).

Measurements below 1 kPa were not recorded by the observers. The three observers made a specific training before starting the enrollment of the patients.
Liver biopsy was performed in outpatients under ultrasound guidance after mild local anelgesia at the level of the right hepatic lobe and frustules were sent for reading to the same pathologist. The degree of liver fibrosis was assessed according to the METAVIR "score system" that includes five stages: F0, no fibrosis; F1, early fibrosis (portal fibrosis without septa); F2, moderate fibrosis (portal fibrosis with few septa); F3, severe fibrosis (numerous septa without cirrhosis); and F4, cirrhosis (24) (Fig. 2)
RESULTS

The “real time” Shear Wave Elastosonographic evaluation of the hepatic parenchyma had technical success in 90/94 patients (96%). The technical failure in four patients was due in two patients to the fact that the intercostal space was too narrow to obtain an optimal scan window for correct measurements and in two patients to the fact that they could not hold a proper breathing at the time of measurements. In the group of healthy volunteers, the mean values of the measurements of liver parenchyma were 5.5 ± 0.7 kPa (standard deviation) with a range of 3.7 to 6.7 kPa. Males showed significantly higher values than females (respectively 5.7 kPa ± 0.5 vs 5.4 ± 0.7 kPa; P = 0.02) (Fig. 3).

In the group of patients with chronic viral hepatitis B or C, the average values of measurements liver parenchyma ranged between 4.3 and 40.5 kPa (Fig. 4).

The elastosonographic evaluation of the liver parenchyma showed a good correlation with the results of the biopsy relatively to the stage of fibrosis (p <0.001). Measurements of liver parenchyma showed some overlap between degrees F0 and F1, while a clear distinction between the degrees F2 (P = 0.002), F3 (P = 0.1) and F4 (P = 0.001). The evaluation of liver parenchyma showed overall diagnostic accuracy of 86% - 98% and a specificity of 90% - 93%. In 3 cases a discrepancy was documented between the given elastosonographic and the bioptic results. In two cases, the elastosonographic
evaluation underestimated the degree of fibrosis by one stage; in one case, the elastosonographic evaluation overestimated the degree of fibrosis by one stage. Finally, an excellent reproducibility was observed in the measurements between the three observers (ICC, 0.85; 95% confidence interval: 0.70 to 0.94) (Fig. 5).
DISCUSSION

Patients with chronic viral hepatitis B and C are at high risk of developing liver cirrhosis. The evaluation of fibrosis has important prognostic and therapeutic implications (25,2). Although the liver biopsy still represents the gold standard method for the diagnosis and staging of fibrosis and cirrhosis of the liver, it is an invasive approach that is associated to a significant risk of complications. Liver biopsy, is also not a perfect method for the surveillance of this patient population.

The ultrasound elastography methods have been recently introduced in the clinical practice. They measure the elasticity of tissue non-invasively. They are based on the compression of the tissue examined which produces a displacement/distortion within the same tissue, with subsequent calculation of the profile of the deformation along the axis of compression; the profile of displacement/distortion represents the distribution of elasticity of the tissue examined and consequently its degree of greater or lesser elasticity and is generally expressed in kPa (Fig. 6). Elastosonographies techniques are proposed as an alternative to liver biopsy for diagnosis and staging the degree of liver fibrosis and its surveillance. In particular, the Transient Elastography, the “real time” Share Wave Elastography and the “real time” Acoustic Radiation Force Impulse are currently the three techniques of greater use in direct and indirect measurement of liver stiffness, ie the degree of liver fibrosis (26-30). Among these techniques, the Fibroscan is the one used by more time in the clinical pratice with unreliable results in 15.8% of cases.
This study was undertaken to assess the validity of “real time” Share Wave Elastography, i.e., the reproducibility and accuracy of measurements of this method.

While ultrasound elastosonographic imaging is now widely recognized as a reliable method to assess liver fibrosis, various techniques that use Transient Elastography imaging are imprecise for detection of early and intermediate levels of fibrosis (2,24,32). Previous studies reported high accuracy with transient elastography only for detection of the more advanced fibrosis stages F3 and F4 (33). Other results show that “real time” Share Wave Elastography is a highly reproducible method for assessing liver stiffness because it was characterized by very high levels of intraobserver and interobserver agreement, both overall and for single measurements. Moreover, the reproducibility of the method was similar in healthy subjects and in patients with chronic viral hepatitis. Ultrasound imaging techniques are subject to user dependency. Nevertheless, good interobserver agreement rates have been reported for Shear Wave Elastography, suggesting that the method itself has low variability and requires only a short period of training to be performed reliably (34-36). Indeed, the benefits of image guidance will likely reduce the learning curve and the variations between measurements (36).

The results of this study show that “real time” Shear Wave Elastography results are directly and linearly correlated with the stages of fibrosis determined using histology.
The diagnostic accuracy of “real time” Shear Wave Elastography was similar to that reported by some other studies, which used a different Shear Wave Elastography method that also included Acoustic Radiation Force Impulse.

Rizzo et al (14) found that Acoustic Radiation Force Impulse was more accurate than Transient Elastography for the staging of both significant and severe liver fibrosis. However, those results were not confirmed by a recent meta-analysis that compared Acoustic Radiation Force Impulse with Transient Elastography and found comparable diagnostic accuracies of both methods for the diagnosis of severe fibrosis and a slightly but significantly higher diagnostic accuracy of Transient Elastography for the diagnosis of significant fibrosis and cirrhosis (15).

“Real time” Shear Wave Elastography is a recently developed method that is part of second generation ultrasound elastography methods.
CONCLUSION

In conclusion "real time" Shear Wave Elastosography showed to be a reproducible method and accurate in measuring the stiffness of the liver parenchyma in patients with chronic liver disease and in the group of healthy volunteers. Healthy volunteers showed significantly lower values with respect to patients with chronic liver disease.
Figures

1) An example of final screenshot at the end of procedure
2) Metavir Score System
3) Liver stiffness in female and in male patients

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4) Liver stiffness values in patient with chronic viral B liver disease
5) “Real time” Share Wave Elastography vs. bioptic findings
6) Share Wave Elastography Imaging Analysis and its propagation map
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